FirstDiscovery Command Reference Manual

Impact: Integrated Modeling Program using Applied Chemical Theory
Version 3.0, June 2004

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Impact ™ contact:

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FirstDiscovery Version 30511
June 2004

1 Introduction to FirstDiscovery

Impact™ (Integrated Modeling Program using Applied Chemical Theory), the heart of Schrödinger's FirstDiscovery™ modeling suite, is an integrated program for molecular mechanics simulations. It allows the user to define the simulation system (usually a protein or DNA molecule in aqueous solution) and to perform Monte Carlo or molecular dynamics simulations. In addition, the user has at her/his disposal a whole array of tools for analyzing the results of the simulations. Finally, Impact is the "driver" for the high-throughput ligand screening program Glide™, the Liaison™ module for calculating ligand binding energies, and the mixed mode Quantum Mechanics/Molecular Mechanics program QSite™.

This is the *FirstDiscovery Command Reference Manual*. It documents using Impact from the command-line, and all the keywords of Impact input files. Running FirstDiscovery from Maestro, and discussion of the principal applications Glide, Liaison, and QSite, are more fully documented in the other FirstDiscovery manuals:

- *FirstDiscovery Quick Start Guide*

  A collection of tutorial examples that illustrate Glide, Liaison and QSite.

- *FirstDiscovery User Manual*

  A presentation of FirstDiscovery especially focussed on its Maestro interface.

- *FirstDiscovery Technical Notes*

  A collection of case studies elaborating on the scientific methods and results of Glide, Liaison, and QSite.

1.1 A Brief History of Impact

The current commercial FirstDiscovery suite was developed from the academic Impact originally designed in the laboratory of Professor Ronald M. Levy at Rutgers University. The following people have contributed to the development of FirstDiscovery and Impact:

1.1.1 Commercial Versions

- v3.0 (June 2004) Jay Banks, Yixiang Cao, Wolfgang Damm, Richard Friesner, Emilio Gallicchio, Thomas Halgren, Ronald Levy, Daniel Mainz, Rob Murphy, and Matt Repasky.
- v2.7 (October 2003) Jay Banks, Yixiang Cao, Wolfgang Damm, Richard Friesner, Emilio Gallicchio, Thomas Halgren, Ronald Levy, Daniel Mainz, Rob Murphy, and Matt Repasky.

- v2.5 (January 2003) Jay Banks, Yixiang Cao, Wolfgang Damm, Richard Friesner, Emilio Gallicchio, Thomas Halgren, Ronald Levy, Daniel Mainz, and Rob Murphy.
- v2.0 (June 2002). Jay Banks, Yixiang Cao, Wolfgang Damm, Richard Friesner, Emilio Gallicchio, Thomas Halgren, Ronald Levy, Daniel Mainz, and Rob Murphy.
- v1.8 (September 2001). Jay Banks, Yixiang Cao, Wolfgang Damm, Richard Friesner, Emilio Gallicchio, Thomas Halgren, Ronald Levy, Daniel Mainz, and Rob Murphy.
- v1.7 (March 2001). Jay Banks, Yixiang Cao, Richard Friesner, Emilio Gallicchio, Thomas Halgren, Ronald Levy, Daniel Mainz, Rob Murphy, and Ruhong Zhou.
- v1.6 (November 2000). Jay Banks, Michael Beachy, Yixiang Cao, Richard Friesner, Emilio Gallicchio, Ronald Levy, Daniel Mainz, Rob Murphy, and Ruhong Zhou.
- v1.0 (June 1999). Jay Banks, Richard Friesner, Emilio Gallicchio, Avijit Ghosh, Ronald Levy, Rob Murphy, Anders Wallqvist, and Ruhong Zhou.
- v0.95 (Nov 1998). Jay Banks, Richard Friesner, Emilio Gallicchio, Avijit Ghosh, Ronald Levy, Rob Murphy, Anders Wallqvist, and Ruhong Zhou.
- v0.9 (Aug 1998). Jay Banks, Mark Friedrichs, Richard Friesner, Emilio Gallicchio, Avijit Ghosh, Ronald Levy, Rob Murphy, Anders Wallqvist, and Ruhong Zhou.
- v0.8 (May 1998). Jay Banks, Chris Cortis, Shlomit Edinger, Mark Friedrichs, Richard Friesner, Emilio Gallicchio, Avijit Ghosh, Ronald Levy, Rob Murphy, Anders Wallqvist, and Ruhong Zhou.

1.1.2 Academic Versions

- V7.0 (August 1996). Jay Banks, Yanbo Ding, Gabriela Del Buono, Francisco Figueirido, Ronald Levy, and Ruhong Zhou.
- V6.0 (January 1994). Les Clowney, Francisco Figueirido, Ronald Levy, Lynne Reed, Maureen Smith-Brown, Asif Suri and John Westbrook.
- V5.8 (December 10, 1991). Les Clowney, Francisco Figueirido, Douglas Kitchen, Ronald Levy, Maureen Smith, Asif Suri and John Westbrook.
- V5.7 (December 17, 1990). Steve Back, Teresa Head-Gordon, Douglas Kitchen, Dorothy Kominos, Ronald Levy and John Westbrook.
- V5.5 and earlier (June 1990). Steve Back, Donna Bassolino, John Blair, Fumio Hirata, Douglas Kitchen, David Kofke, Dorothy Kominos, Ronald Levy, Asif Suri and John Westbrook.

1.2 Major Features

The major features of Impact include:

- Build Protein/DNA/RNA from Residue Sequences
- Energy Minimization
- Molecular Dynamics
- Monte Carlo Methods
- Fast Multipole Method (FMM)
- Multiple Time-step Algorithm r-RESPA
- S-Walking/J-Walking Methods
- Explicit Solvation Model
- Poisson-Boltzmann Continuum Solvation (PBF)
- Surface Generalized Born Solvation Model (SGB)
- OPLS-AA with Automatic Atomtype Recognition
- Flexible Schemes for Freezing Part of System
- QSite: Mixed-Mode QM/MM Simulations for Reactive Chemistry
- Liaison: Calculating and Predicting Ligand Binding Energies
- Glide: High-Throughput Ligand-Receptor Docking

1.3 Hardware Requirements

Schrödinger tests and distributes FirstDiscovery 3.0 for SGI IRIX, IBM AIX, and Intel-x86 compatible Linux-based machines at this time. For current information on other platforms, please contact Schrödinger.

1.4 Installation

To install FirstDiscovery please see the *Schrödinger Installation Guide*. A printed version of this manual and other documentation should come with your CD-ROM. PostScript, PDF, and HTML version for most of the First-Discovery manuals should be on the CD-ROM itself.

For those that want to cut to the chase, installation is often as easy as running:

```
% /bin/sh INSTALL
```

from the CD-ROM, and following the prompts. But please see the *Installation Guide*.

After installation, in the directory specified by your `$SCHRODINGER` environment variable, there should be an Impact directory labelled with the current version number, at this printing, this is '`impact-v30511`'. In that directory, there are seven subdirectories:

`bin/` The executable binary and scripts for running all manner of Impact-based jobs. Since these are platform-dependent, these files are separated into further subdirectories with their platform's designation, e.g. `Linux-x86/`.

`data/` The database parameters for the OPLS, OPLS2000, and AMBER force fields.

`docs/` Electronic versions of the *FirstDiscovery Reference Manual* (this document) are located here.

`lib/` Platform-dependent shared libraries needed by Impact are kept here.

`disabled_lib/`
Disabled shared libraries, moved from the '`lib/`' subdirectory should be kept here. Disabling libraries should only be done within Schrödinger's recommendations.

`samples/` The example files noted in this manual's appendices.

`tutorial/`
Files that correspond to the instructional material in the *FirstDiscovery Quick Start Guide* that walks you through various types of `FirstDiscovery` calculations.

A file '`compatibility`' is also in your '`impact-v30511`' directory, listing the minimum version numbers of other Schrödinger products compatible with this FirstDiscovery release. All Schrödinger startup scripts will use this information automatically.

The single important environment variable each Impact user has to have is `$SCHRODINGER`. It should be set to your top-level installation directory for Schrödinger products, e.g. `/usr/local/bin/schrodinger`. If you plan on using some of the utility scripts from a command-line interface, you might like to add the directory `$SCHRODINGER/utilities` to your `PATH` enviroment variable, so that the scripts in this directory are accessible by name without the full directory name prepended. If your command-line shell is `sh`, `ksh`, or `bash`, this is done by:

```
(sh/ksh/bash)% export PATH=$PATH:$SCHRODINGER/utilities
```

and if your shell is `csh` or `tcsh`, then do:

```
(csh/tcsh)% setenv PATH $PATH:$SCHRODINGER/utilities
```

To run a FirstDiscovery example, first make sure that `$SCHRODINGER` is set to your Schrödinger installation directory. Then `cd` to one of example directory and type:

```
% $SCHRODINGER/impact -i input_file -o log_file
```

This will read from the *input_file* and write the log file to *log_file*. If `-o` is not specified, Impact will set the log file name to be the same as your input file, but with a `.log` extension in place of `.inp`.

Note that the log file (*stdout*) is not the file specified in the top `write` command in the input file, which is usually more detailed than the log file. Just typing `impact` with no arguments is equivalent to typing `main1m`: the program then looks for an input file named '`fort.1`', and writes to standard output.
If an input file is specified but a log file is not, Impact constructs the log file name by appending the suffix `.log` to the input file name, after first removing the suffix `.inp` if it is present. Thus

```
% $SCHRODINGER/impact -i myfile
```

and

```
% $SCHRODINGER/impact -i myfile.inp
```

will both result in writing a log file called `myfile.log`.

1.5 Input Files

Instructions for Impact are placed in the *main input file*, which is then given as the `-i` argument to the `impact` execution script.[1] The program executes commands in the input file sequentially, or as directed by control structures in Impact's input scripting language, DICE. See Chapter 5 [Advanced Input Scripts], page 185, for details of control structures, variables, and advanced features of DICE. Here is a simple example:

```
!! MAININPUT  tutor.inp tutor.inp  Main input file
!! MAINOUTPUT tutor.out tutor.out  Main output file
!! INPUT paramstd paramstd           Energy parameter file
!! INPUT tip4p.con tip4p.con         Energy constraints
!! INPUT tip4p.rst tip4p.rst         Coordinate and velocity restart file
!! DESCRIPTION FILE tutor.des
!! TITLE Tutorial example

WRITE file tutor.out -
   title TIP4P Water MD *

CREATE
   build solvent name solvent1 type tip4p nmol 216 h2o
QUIT

SETMODEL
   setpotential
      mmechanics
   quit
```

[1] Historically, the main input file had to be assigned to FORTRAN unit number 1, which usually as the filename '`fort.1`'. The name may be different on other machines.

```
   read parm file paramstd noprint
   enrg parm cutoff 9.5 listupdate 10 diel 1.0 nodist
   enrg periodic name solvent1 bx 18.6353 by 18.6353 bz 18.6353
   enrg cons read file tip4p.con
   enrg molcut name solvent1
QUIT

DYNAMICS
  input cntl -
      nstep 1000 delt 0.001 stop rotations -
      constant totalenergy nprnt 50 tol 1.e-7
  read restart coordinates and velocities box real8 -
    formatted file tip4p.rst
  run
QUIT

END
```

The input file always begins with a description of where to write the output generated by Impact during its execution, and ends with the keyword `end` on a single line. The following meta-example is the simplest legal Impact program:

```
write file fname title your_favorite_title *
end
```

An optional `verbose` *value* argument before the `*` specifies the verbosity of output from various parts of Impact.

After the opening `write` statement, one specifies a sequence of *tasks* that Impact should execute. In Impact tasks correspond to a high-level description of the computer experiment. For example, the task `create` sets up the internal variables describing the molecular structure of the system of interest, while inside of task `dynamics` one runs a molecular dynamics simulation. Typically it is important that tasks are executed in the correct order, which is usually dictated by common sense (the least common of the senses).[2]

A task by itself does not produce any side effects. For instance, the fragment

```
create
quit
```

would do exactly nothing. When Impact begins executing a task it sets up a special environment, which is task-dependent. This environment exists until the keyword `quit` is encountered, closing the task. Within each of these environments different collections of commands (subtasks) are in effect. For instance, within the `create` task one can execute the subtask `build`, but it

[2] For example, few people we know would run a dynamics simulation before setting the system up.

is not defined inside of the task `dynamics`. Trying to execute `build` inside of the latter task would lead to an error.

Impact requires that tasks (as well as their matching `quit`) be declared on a line by themselves. Subtasks, on the other hand, come in several flavors. They must always be the first non-blank word on a line and most often they are followed on the same line by a series of subtask-specific keywords and parameter values. A few, however, have the same formatting requirements as tasks do, and must be ended by the keyword `quit`.[3]

In general, task and subtask names can be abbreviated by giving the first four characters of the full name. In addition, some special abbreviations are recognized. For example: `minimize` can be entered as `minm`; `energy` can be given as `enrg` (as illustrated above); . . .

Because Impact is written mostly in FORTRAN the implementation puts a limit on the maximum length of a line of 2000 characters. As the lines are scanned lowercase letters are automatically converted to uppercase, unless protected as shown below.[4] The following characters are special:

‘`"`’ To protect a word and preserve the case. For example, if you want to open a file named ‘`/home/me/FooBar`’, you must write ‘`"/home/me/FooBar"`’.

‘`!`’ An exclamation point ‘`!`’ flags a comment, and anything following it until the end of the line is not read or processed.

‘`-`’ A hyphen at a line’s end indicates the command is continued on the next line of the input file. Note that there should be at least one space before the hyphen and that the sum of the lengths of the continued lines must not exceed the limit of 2000 characters.

‘`$`’ String constants are delimited by this character as in ‘`$foo$`’.

‘`’`’ The quote is used to delimit names of variables used in Impact input files, as in ‘`while 'foo' lt 10`’.

‘`*`’ Sometimes *portions* of command lines are terminated with an asterisk. It is required wherever it appears in the examples. This character is also used as a wild-card in some strings used to access tables (see Section 4.4 [Table (analysis)], page 175).

The top level of Impact is the *task* level where the objects of primary interest are described, such as system creation, molecular dynamics or energy minimization. When describing *tasks* in this documentation, meta-examples are generally used, where the following conventions are followed. The order of the keywords inside a subtask is generally not important though, of course, a keyword cannot be separated from its value when one is required.

[3] They act like secondary level tasks.

[4] File names that are not protected are actually converted back to lowercase before opening the file.

`keywords` that should be typed exactly as shown will appear in this font. Some keywords may be abbreviated by an initial portion of the word, and the examples in this manual contain some such abbreviations; but in the absence of such an example, use the entire keyword as shown.

variables are meta-keywords, that is, you must replace *variable* with the appropriate `keyword`, number, or filename.

`[ ]` is used to delimit keywords that are optional; an extra character, '`+`' or '*', may also be present. `[ ]+` means to repeat the contents one or more times and `[ ]*` to repeat the contents zero or more times.[5] For example

```
[ foo | bar | baz ]
```

means that one of the keywords `foo` or `bar` or `baz` may be used in this location. If there are no '`|`' characters present the body is always optional, and if there is a a '`+`' immediately following the ']', as in '`[ foo ]+`', then repeat the contents 1 or more times (here 1 or more occurrences of `foo`).

nil stands for the "empty item," that is, no item at all, so that '`[` *foo* `|` nil `]`' is equivalent to '`[` *foo* `]`'.

`( )` in an example indicates that the contents of the parentheses is repeated as many times as indicated by the following expression. In the following expression the symbols '`foo bar baz`' are repeated four times.

```
( foo bar baz ) repeated four times
```

Using the above rules, the meta-example

```
You should [ run | debug ] Impact [ when it rains | nil ]
```

is expanded in any of the following statements

```
You should run Impact when it rains
You should debug Impact when it rains
You should run Impact
You should debug Impact
```

One instance of a meta-example for the minimization task is:

```
minimize
   read restart coordinates formatted file fname
   steepest dx0 value dxm value deltae value
   run
   write restart coordinates formatted file fname
```

[5] The other potential uses of the square brackets are discussed in Section 5.1.1 [Lists (Background)], page 186.

```
quit
```

where *value* refers to the value to be assigned to the preceding keyword, and *fname* refers to a file name.[6]

Some keywords are common to many different tasks and subtasks, so they are described here.

`file` This keyword must be followed by the name of a file. In the meta-examples this is generally shown as *fname*.[7]

`name` This keyword must be followed by the name of a species. In the meta-examples this is generally shown as *spec*.

`resnumber`
This keyword must be followed by the number (integer value) of a residue. In the meta-examples this is generally shown as *resn*. It should be noted that residue numbers supplied in the main input file have the following meanings: positive numbers mean the residue numbering used in the original PDB file; negative numbers mean the reordered Impact residue numbers (i.e., sequential, starting with 1); 0 means all applicable residues.

`atname` This keyword must be followed by the name (character string) of an atom. In the meta-examples this is generally shown as *atna*.

`fresidue`

`lresidue` These keywords should be followed by a number specifying the first and last residues of interest in the primary sequence.

`echoon`

`echooff` These keywords can appear at the task level, or the subtask level of task `analysis`. They turn on or off the printing of certain output. The default is `echoon`.

An aid to gauging the correctness of an input file is that, in general, as each command is processed it is deleted from the command line. When processing is finished, a check is made to see that no characters remain. The presence of extraneous characters indicates that the input file was incorrectly formed.

This document frequently refers to input files that may be used as examples. For example, in Section C.3.3 [Trajectory (example)], page 275, a system of formaldehyde in water is first created and molecular dynamics is performed and a trajectory file is created. The trajectory is subsequently read, and statistics are gathered on the full dynamics run.

---

[6] Value and number are **usually** equivalent to real and integer. *Val* or *num* are also used in this context.

[7] To refer to the file '`junk`' you would type '`file junk`'.

1.6 Structure File Formats

Via the `build primary type auto` (see Section 2.2.1.5 [Auto (primary type)], page 24) and `build types` (see Section 2.2.1.11 [Types (build)], page 30) commands, Impact can read and write Maestro, MDL SD, and PDB files.

Historically, Impact used PDB file formats for all input structure files, and this is *still* required for the AMBER86 force field. Other file formats have to be converted into PDB files first before any Impact simulations can be performed in such situations.

The freely available program `Babel` is a program that converts different file formats, and currently supports input file formats:

```
Input file type

  1. Alchemy                    2. AMBER PREP
  3. Ball and Stick             4. MSI BGF
  5. Biosym .CAR                6. Boogie
  7. Cacao Cartesian            8. Cambridge CADPAC
  9. CHARMm                    10. Chem3D Cartesian 1
 11. Chem3D Cartesian 2        12. CSD CSSR
 13. CSD FDAT                  14. CSD GSTAT
 15. Dock PDB                  16. Feature
 17. Free Form Fractional      18. GAMESS Output
 19. Gaussian Z-Matrix         20. Gaussian Output
 21. Hyperchem HIN             22. MDL Isis
 23. Mac Molecule              24. Macromodel
 25. Micro World               26. MM2 Input
 27. MM2 Ouput                 28. MM3
 29. MMADS                     30. MDL MOLfile
 31. MOLIN                     32. Mopac Cartesian
 33. Mopac Internal            34. Mopac Output
 35. PC Model                  36. PDB
 37. JAGUAR Input              38. JAGUAR Output
 39. Quanta                    40. ShelX
 41. Spartan                   42. Spartan Semi-Empirical
 43. Spartan Mol. Mechanics    44. Sybyl Mol
 45. Sybyl Mol2                46. Conjure
 47. UniChem XYZ               48. XYZ
 49. XED                       50. M3D
```

and output file formats:

```
Output file type

  1. DIAGNOTICS                 2. Alchemy
```

```
 3. Ball and Stick              4. BGF
 5. Batchmin Command            6. Cacao Cartesian
 7. Cacao Internal              8. CAChe MolStruct
 9. Chem3D Cartesian 1         10. Chem3D Cartesian 2
11. ChemDraw Conn. Table       12. MSI Quanta CSR
13. Dock Database              14. Wizard
15. Conjure Template           16. CSD CSSR
17. Feature                    18. Fenske-Hall ZMatrix
19. Gamess Input               20. Gaussian Cartesian
21. Gaussian Z-matrix          22. Gaussian Z-matrix tmplt
23. Hyperchem HIN              24. Icon 8
25. IDATM                      26. Isis
27. Mac Molecule               28. Macromodel
29. Micro World                30. MM2 Input
31. MM2 Ouput                  32. MM3
33. MMADS                      34. MDL Molfile
35. Mopac Cartesian            36. Mopac Internal
37. PC Model                   38. PDB
39. JAGUAR Z-Matrix            40. JAGUAR Cartesian
41. Report                     42. Spartan
43. Sybyl Mol                  44. Sybyl Mol2
45. MDL Maccs file             46. XED
47. UniChem XYZ                48. XYZ
49. M3D
```

Before you run `babel`, you need to setup an environmental variable $BABEL_DIR:

```
% setenv BABEL_DIR your_babel_directory
% export BABEL_DIR= your_babel_directory
```

The easiest way to run `babel` is in manual mode:

```
% babel -m
```

and follow instructions to select desired input and output file formats. You can also run `babel` from the command line, as in

```
% babel -ix myfile.xyz -renum -oai myfile.dat "AM1 MMOK T=30000"
```

This will create a MOPAC input file with atom 1 from *myfile.xyz* as atom 1 in *myfile.dat*. For details of how to run `babel`, etc, consult the README files under the `babel` directory. `babel` also comes with Schrödinger's product Jaguar, and is accessible therein via the `jaguar babel` command.

1.7 Force Field

In molecular modeling there are several different force fields used to describe the interactions among atoms and molecules. Some of the well known ones are OPLS, MMFF, AMBER, MM3, CHARMm, and GROMOS. Impact

currently supports OPLS-AA[8] and AMBER86[9]. Both force fields are applicable to protein simulations, but only OPLS-AA is applicable to ligand (or protein-ligand) simulations, and only AMBER86 is applicable to DNA/RNA simulations. These two force fields are described in more detail below, along with a polarizable OPLS force field methodology under active development in Schrödinger.

1.7.1 OPLS-AA

The OPLS-AA force field, which was developed by the Jorgensen group, is an effort to develop a parameterization that reproduces liquid state properties of molecules. Again this is a force field that uses experimental data from the liquid state and quantum mechanical calculations for intramolecular bond, angle, and torsion motions to set the constituent parameters. The intramolecular interaction is given as,

$$V_{\text{intra}} = \sum_{\text{bonds}} K_r(r - r_{eq})^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_{eq})^2 + V_{\text{torsion}}$$

written as,

$$V_{\text{torsion}} = \sum_i \frac{V_1^i}{2}\left[1 + \cos(\phi)\right] + \frac{V_2^i}{2}\left[1 - \cos(2\phi)\right] + \frac{V_3^i}{2}\left[1 + \cos(3\phi)\right].$$

The non-bonded interaction is given as a van der Waals terms together with an electrostatic term (R is again the atom-atom distance),

$$V_{\text{inter}} = \sum_{i<j}\left[4\epsilon_{ij}\left(\frac{\sigma_{ij}^{12}}{R_{ij}^{12}} - \frac{\sigma_{ij}^{6}}{R_{ij}^{6}}\right) + \frac{q_i q_j}{R_{ij}}\right].$$

Note that in this description the dielectric constant is set to its proper value of 1.0. For molecules containing atoms connected by a distance of more than 3 bond-lengths the atom-atom interaction is given by the V_{inter} -term. The (1,4)-interactions are scaled by a factor of 1/2. The non-bonded parameters ϵ and σ for each atom-pair is constructed from the atomic values by the geometric mean combination rule,

$$\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j}$$
$$\sigma_{ij} = \sqrt{\sigma_i \sigma_j}.$$

It is also possible to use the partial charges read from a Maestro or MacroModel format structure file instead of those provided by OPLS-AA, using the `cmae` keyword documented in Section 2.2.1.5 [Auto (primary type)], page 24.

[8] W. L. Jorgensen, D. S. Maxwell, and J. Tirado-Rives, *J. Amer. Chem. Soc.*, **118**, *11225–11235* (1996)

[9] S. J. Weiner, P. A. Kollman, D. T. Nguyen, and D. A. Case, *J. Comput. Chem.*, **7**, *230–252* (1986)

1.7.2 AMBER86

The AMBER86 force field developed by Kollman and co-workers provides a general description of the intra- and intermolecular interactions. All the atoms are treated explicitly. Although the form of the force field is very general, this force field is chiefly designed to be applied in in the area of molecular biology and thermodynamics of small organic molecules. Given a set of coordinates of the system the total potential energy is calculated from

$$V_{\text{total}} = V_{\text{intra}} + V_{\text{inter}}$$

where the intramolecular energy is schematically written as

$$V_{\text{intra}} = \sum_{\text{bonds}} K_r(r - r_{eq})^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_{eq})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)]$$

and the non-bonded or intermolecular term is likewise written as

$$V_{inter} = \sum_{i<j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\epsilon R_{ij}} \right] + \sum_{\text{H}-\text{bonds}} \left[\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}} \right].$$

The atom-pair distance is denoted R_{ij} and the sum runs over all unique atom pairs. This force field is semi-empirical, i.e., the parameters are derived partly from experimental data (non-bonded terms) and partly from quantum chemical calculations (intramolecular terms). It also contains an empirical model of the dielectric constant ϵ modeled as a distant dependent quantity where $\epsilon(R_{ij}) = R_{ij}$. For molecules containing atoms connected by a distance of more than 3 bond-lengths the atom-atom interaction is given by the V_{inter} -term. However, interactions separated by exactly 3 bond-lengths (1,4-interactions) are scaled by a so called 1,4-scaling factor. A factor of 1/2 is used for both Lennard-Jones and Coulombic interactions. The non-bonded parameters A_{ij} and B_{ij} are constructed by combination rules from a set of van der Waals parameters for the constituent atoms

$$A_{ij} = \sqrt{A_i A_j}$$
$$B_{ij} = \sqrt{B_i B_j}.$$

The C_{ij} and D_{ij} are explicitly given for all hydrogen bonded cases.
The AMBER86 force field is superseded by the AMBER95 and later force fields developed by the Kollman group. AMBER95 omits all explicit hydrogen bond terms. However, Impact does not support AMBER95 or later force fields in the AMBER series.

1.7.3 PFF

The PFF module is only available under special license from Schrödinger.

The Polarizable Force Field (PFF) is under continuing development at Schrödinger. For details consult the papers by Banks et al.[10], and by Stern et al.[11]

A brief description from Stern is presented below.

Consider a polarizable system represented by fluctuating charges q_A on a set of atoms A and induced dipoles $\vec{\mu}_B$ on a (possibly overlapping or identical) set of atoms B. The system is also subject to an "external" electrostatic potential $\phi^0(\vec{r})$ with gradient $-\vec{E}^0(\vec{r})$. The superscript zero denotes that this electrostatic potential and field do not arise from the fluctuating charges or dipoles, but from some other source, for instance, a set of fixed charges.

Each fluctuating charge q_A has a self-energy $\chi_A q_A + \frac{1}{2} J_A q_A^2$, where χ_A and J_A are parameters corresponding to the atomic electronegativity and hardness.[12] The interaction with the external potential gives a term $\phi_A^0 q_A$ where ϕ_A^0 is the value of the external potential at site A. Pairs of fluctuating charges $q_A, q_{A'}$ give rise to an interaction energy $q_A J_{AA'} q_{A'}$ where $J_{AA'}$ depends on the distance between sites A and A'. For instance, if we assume the interaction is Coulombic, then

$$J_{AA'} = \frac{1}{|\vec{r}_{AA'}|},$$

where $\vec{r}_{AA'} = \vec{r}_A - \vec{r}_{A'}$ is the displacement vector from site A' to site A.

The dipolar terms are quite similar. If α_B is the polarizability tensor for atom B, then an induced dipole $\vec{\mu}_B$ has a self-energy[13] $\frac{1}{2}\vec{\mu}_B \cdot \alpha_B^{-1} \cdot \vec{\mu}_B$. In addition, $\vec{\mu}_B$ interacts with the external field giving a term $-\vec{E}_B^0 \cdot \vec{\mu}_B$, where $\vec{E}_B^0$ is the value of the field at site B. Pairs of dipoles $\vec{\mu}_B, \vec{\mu}_{B'}$ give rise to an interaction energy $\vec{\mu}_B \cdot \mathcal{J}_{BB'} \cdot \vec{\mu}_{B'}$, where $\mathcal{J}_{BB'}$ depends on the locations of sites B and B' and must be a dyadic so that the interaction energy is independent of the choice of coordinate system. If we assume the interaction is Coulombic, then

$$\mathcal{J}_{BB'} = \frac{1}{|\vec{r}_{BB'}|^3}\left(1 - 3\frac{\vec{r}_{BB'}\,\vec{r}_{BB'}}{|\vec{r}_{BB'}|^2}\right)$$

Finally, the fluctuating charges and dipoles interact (if they are on different sites). Each pair of fluctuating charges $q_A, \vec{\mu}_B$ gives an interaction energy

[10] J. L. Banks, G. A. Kaminski, R. Zhou, D. T. Mainz, B. J. Berne, and R. A. Friesner, *J. Chem. Phys.* **110**, *741* (1999)

[11] H. A. Stern, G. A. Kaminski, J. L. Banks, R. Zhou, B. J. Berne, and R. A. Friesner, *J. Phys. Chem. B*, **103**, *4730* (1999)

[12] S. W. Rick, S. J. Stuart, and B. J. Berne, *J. Chem. Phys.*, **101**, *6141*, (1994); A. K. Rappé and W. A. Goddard III, *J. Phys. Chem.*, **95**, *3358*, (1991).

[13] P. Ahlström, A. Wallqvist, S. Engström, and B. Jönsson, *Mol. Phys*, **68**, *563* (1989)

$q_A \, \vec{J}_{AB} \cdot \vec{\mu}_B$. As before $\vec{J}_{AB}$ depends on the locations of sites A and B and in this case is a vector. Assuming the interaction is Coulombic,

$$\vec{J}_{AB} = \frac{\vec{r}_{AB}}{|\vec{r}_{AB}|^3}.$$

The total electrostatic energy due to the fluctuating charges and dipoles may therefore be written

$$U = \sum_A (\chi_A + \phi_A^0)\, q_A - \sum_B \vec{E}_B^0 \cdot \vec{\mu}_B + \frac{1}{2} \sum_A J_A \, q_A^2 + \frac{1}{2} \sum_B \vec{\mu}_B \cdot \alpha^{-1} \cdot \vec{\mu}_{B'} + \frac{1}{2} \sum_{A \neq A'} q_A \, J_{AA'} \, q_{A'} + \frac{1}{2} \sum_{B \neq B'} \vec{\mu}_B \cdot \mathcal{J}_{BB'} \cdot \vec{\mu}_{B'} + \sum_{AB} q_A \, \vec{J}_{AB} \cdot \vec{\mu}_B.$$

It is convenient to define $J_{AA} \equiv J_A$ and $\mathcal{J}_{BB} \equiv \alpha_B^{-1}$; in this case the energy may be written slightly more simply:

$$U = \sum_A (\chi_A + \phi_A^0)\, q_A - \sum_B \vec{E}_B^0 \cdot \vec{\mu}_B + \frac{1}{2} \sum_{AA'} q_A \, J_{AA'} \, q_{A'} + \frac{1}{2} \sum_{BB'} \vec{\mu}_B \cdot \mathcal{J}_{BB'} \cdot \vec{\mu}_{B'} + \sum_{AB} q_A \, \vec{J}_{AB} \cdot \vec{\mu}_B. \tag{1}$$

Let us now define $N_A + 3N_B$ dimensional vectors $\mathbf{q}$ and $\mathbf{v}$, and an $N_A + 3N_B$ by $N_A + 3N_B$ matrix $\mathbf{J}$, where N_A is the number of fluctuating charges and N_B is the number of dipoles:

$$\begin{aligned} \mathbf{q} &\equiv (q_A, \vec{\mu}_B) \\ \mathbf{v} &\equiv (\chi_A + \phi_A^0, -\vec{E}_B^0) \\ \mathbf{J} &\equiv \left(J_{AA'}, \vec{J}_{AB'}, \vec{J}_{A'B}^{\,\dagger}, \mathcal{J}_{BB'} \right), \end{aligned}$$

Then above equation may be written succinctly as a matrix equation:

$$U = \mathbf{v}^\dagger \mathbf{q} + \frac{1}{2} \mathbf{q}^\dagger \mathbf{J} \mathbf{q}.$$

For any given set of atomic electronegativities χ_A and values for the external potential and field ϕ^0 and $\vec{E}^0$ at the sites A and B, the fluctuating charges and induced dipoles are determined by minimizing eq. (1) with respect to each variable $q_A, \vec{\mu}_B$. It can be seen that in the case of an all-dipole system, this is equivalent to imposing the usual self-consistent field requirement on the induced dipoles. If, as in this case, there are no constraints on the

variables, then minimizing leads to a set of linear equations whose solution is

$$\mathbf{q} = -\mathbf{J}^{-1}\mathbf{v}.$$

Constraints on the fluctuating charges, such as the requirement that each molecule remain neutral, may be handled by the method of Lagrange multipliers, or by a transformation to a reduced set of unconstrained coordinates $\mathbf{q}'$, where $\mathbf{C}^{\dagger}\mathbf{q}' = \mathbf{q}$ for some matrix $\mathbf{C}$. In this case the solution is given by

$$\mathbf{q} = -\mathbf{C}^{\dagger}(\mathbf{C}\mathbf{J}\mathbf{C}^{\dagger})^{-1}\mathbf{C}\mathbf{v}.$$

We note that the response $\Delta\mathbf{q}$ to any additional perturbation $\Delta\mathbf{v}$, for instance, an external, applied electrostatic potential or field from additional charges—is simply

$$\Delta\mathbf{q} = -\mathbf{J}^{-1}\,\Delta\mathbf{v}$$
$$\Delta\mathbf{q} = -\mathbf{C}^{\dagger}(\mathbf{C}\mathbf{J}\mathbf{C}^{\dagger})^{-1}\mathbf{C}\,\Delta\mathbf{v},$$

for unconstrained and constrained coordinates, respectively. The response to external perturbations does not depend on $\mathbf{v}$—that is, on the electronegativities and original fixed charges we have placed in the system. A polarization model for a given molecule therefore involves a specification for the elements of the matrix $\mathbf{J}$, that is, the interactions between pairs of fluctuating charges and dipoles.

1.8 Online Documentation

Schrödinger publishes HTML versions of many product manuals at the website http://www.schrodinger.com/Support/pdf.html. An up-to-date copy of this manual, the *FirstDiscovery Reference Manual*, along with other FirstDiscovery manuals, are linked there.

2 Setup System

This chapter describes tasks to set up Impact simulations: create system, and set up models, etc. This should be done before any real simulation tasks can be performed.

2.1 Set commands

These commands are not true tasks, in that they are completely specified on one line, with no subtasks and no `quit` keyword. They are used to specify conditions of the Impact execution that typically remain the same throughout the duration of the program, so they should usually occur at the beginning of the input file, either immediately after or even before the initial `write` command that specifies the main output file. In particular, `set ffield` may have unpredictable results if it occurs in the middle of an input script, or if two or more `set ffield` commands are issued in the same script.

2.1.1 Set Path

This command specifies a directory where Impact will look for input files specified in subsequent commands. The directory name is added to a list stored in memory. When Impact starts up, the list contains '`.`' (the current working directory), and a default directory that normally is '`$SCHRODINGER/impact-v3.0/data`'. The `set path` command adds **one** directory to the **end** of this list. Thus the specified directory will be searched only for files that cannot be found in the current working directory, the default directory, or directories specified by previous `set path` or `set ffield` commands. To specify more than one directory, use more than one `set path` command, one for each directory in the order you wish them to be searched.

- `set path` *dirname*

2.1.2 Set Ffield (or Set Force)

This command specifies the force field that Impact uses to calculate energies and forces. This has two consequences:

A directory that contains the parameter and residue database relevant to the specified force field is added to the **beginning** of the search path, after only the current working directory. Thus the correct residue and parameter files will be used instead of the default ones.

A flag is set that indicates which force field is being used. This flag determines the functional form used in energy and force calculations.

- `set ffield` *ffname*

Currently the values that can be used for *ffname* are `AMBER86`, as described in Section 1.7.2 [AMBER86 (ffield)], page 13, `OPLS1999`[1], as described in Section 1.7.1 [OPLS-AA (ffield)], page 12, `OPLS2000`, and `OPLS2001` for fixed-charge force fields, as well as `OPLS_PFF_2000` and `OPLS_PFF_2003` for Schrödinger's polarizable force field. `OPLS2001` is the default force field.

`OPLS2000`[2] includes newly optimized torsional parameters for peptides and new non-bonded parameters for sulfur that replace the corresponding parameters of the standard `OPLS` force field. `OPLS2001` uses the same force field parameters as `OPLS1999`, but the atomtyping is done with general SMARTS-based pattern-matching and additional bond type indices for assigning stretch, bend, and torsional parameters.

The residue and parameter files for these force fields are in subdirectories of the default directory. The OPLS functional form is used by default if no `set ffield` command is given.

Caution: QSite has been specifically developed using `OPLS1999`, and QSite jobs will exit with an error if this force field is not specified. Maestro writes the command `SET FFIELD OPLS1999` to the Impact input file for all QSite jobs. Schrödinger recommends that you use `OPLS2001` for basic Impact, Glide, and Liaison simulations.

The current set of residue files for OPLS contains only amino acid residues, water molecules, one ion (chloride), and a few small molecules such as N- and C-terminal "blocker" residues. Nucleic acid and other residues will be added in the future.

`OPLS_PFF_2000` and `OPLS_PFF_2003` select Schrödinger's Polarizable Force Field (see Section 1.7.3 [PFF (ffield)], page 14), with bonded and torsional parameters adapted from one of the fixed-charge force fields and atomtyping schemes `OPLS2000` and `OPLS2003`. In order to use the PFF in a simulation, it is also necessary to include the `pff` keyword in the `SETMODEL` task. See Section 2.3.4.1 [Mmechanics (setpotential)], page 41.

The PFF module is only available under special license from Schrödinger.

2.1.3 Set Noinvalidate

Maestro files can embed properties, such as energies and structure identifiers, that implicitly only correspond to the particular structure, connectivity, or even precise Cartesian coordinates of the atoms. Maestro files can encode these *dependencies* in such a way to tell other Schrödinger software when they are invalid and should be deleted from the structure.[3]

---

[1] `OPLS` is a synonym for `OPLS1999`.

[2] G. A. Kaminski, R. A. Friesner, J. Tirado-Rives and W. L. Jorgensen, *J. Phys. Chem. B*, **105**, *6474–6487* (2001)

[3] These dependencies are denoted by a `m_depend` block in Maestro files.

For example, if an input structure already has a property `r_mmod_Potential_Energy-OPLS-AA`, this is an energy that corresponds to the particular geometry of the molecule. If any of the internal coordinates are changed, the energy value is no longer valid. FirstDiscovery removes such properties if and when it modifies geometries, and upon output of the structure, they will not appear.

Sometimes, however, it is desired to retain all the input properties through a complicated workflow. Perhaps you have minimized a number of ligand structures with MacroModel, and then dock them with Glide using its internal conformation generator. Normally, when Glide does its conformation generation, it invalidates all the input properties known to depend on the internal coordinates of the structure, including the MacroModel energies. If you want your output PoseViewer files to keep these properties, even if they don't correspond to the coordinates anymore, and also have the Glide pose properties, which do correspond, then you must add this `set noinvalidate` property to your Glide input file.

- `set noinvalidate`

Caution: This option is a temporary measure. In the future, we intend to introduce an easy-to-use method in Maestro to tailor each property's invalidation setting, so you can clear invalid ones while fixing other ones, to your preference.

2.2 Task Create

The object of this task is to set up, modify and process the internal coordinates of the molecules in the simulated system. Very few things can be done without first setting up the system, so this task is typically among the first to be executed. Remember, however, that Impact input files should start with a line that identifies the name of the log file and a descriptive title. Thus, the typical Impact input file has the structure

`write file` *logfile* `title` Some title `*`
`set` commands if desired
`create`
  Set up the simulation system
`quit`
`setmodel`
  Set up the model parameters
`quit`
Perform the calculations
`end`

2.2.1 Subtask Build

This subtask is used to initialize or modify the connectivity arrays, internal and cartesian coordinate arrays, residue arrays, and charge arrays for the molecule(s) specified by the user. The modification may be a conformational change (i.e., a change in secondary structure), or the insertion of connectivity information (for crosslinks), or the addition of a user defined residue into a molecule. '`Build primary`' must be called before any further calculations to fill the arrays.

2.2.1.1 Primary

This option builds up a protein (or peptide) molecule from a list of amino acids, or DNA or RNA from a list of nucleotides. It builds up the primary sequence by, for example, filling the connectivity arrays using a residue data base containing all standard L-amino acids and nucleotides. Default internal cartesian coordinate arrays are also filled by using equilibrium bond lengths and angles, which are obtained from the all-atom residue data base. All side chain torsion angles for proteins are initially trans (defined as 180 degrees). The options are described below, where *D* in *D-nucleotides* is deoxy, and *R* is ribo.

2.2.1.2 Primary type Protein

- `build primary name` *spec* `type [ protein | other ] -`
  `[` *residue_list* `end | read file` *fname* `] -`
  `[ sidechain neut [ all | acid | base ] ] -`
  `( chainname` *chain_name* `)` repeat for all chains `-`
  `[ [ substitute` *resn1* `to` *resn2* `[ rnumber` *resn* `] ] ]* -`
  `[ crosslink name` *spec* `[ file` *fname* `] -`
  `[ rname` *resna* `aname` *atna* `rname` *resna* `aname` *atna* `]+ -`
  `[ cut` *cutoff_distance* `] ] [print]`

  Builds the molecular structure for a protein or user-defined (`other`) molecular species. The structure can be either specified by an optional list of three-letter residues (see Appendix A) or read from a PDB file. The structure need not be contiguous, i.e., in one chain. One can specify a break in the sequence, which starts a new chain, by specifying '`***`' instead of the name of a residue. For each chain one can also specify a name through which it will be identified later. For instance,

```
build primary name peptide1 type protein ala ala gly ser leu end
```

  would build a small peptide with five amino acids (only one chain) and

```
build primary name peptide2 type protein -
    ala gly ser leu *** ser ser ala end -
    chainname A chainname B
```

would construct a two-chain heterodimer where the first chain is named '`A`' and the second '`B`'.[4]

If a file to be read is specified, it must be a PDB file; Impact will construct the primary sequence as directed there. Otherwise the sequence will be built using *residue_list*. **Caution:** Building a protein using amino acid templates works only with `set ffield amber86` and `set ffield opls`, and not with the default OPLS2001 force field (see Section 2.1.2 [Set ffield], page 17).

The program is also capable of specifying that sidechains be neutralized to respond to various local pH environments. The default is to use ionized sidechains for LYS, ARG, ASP and GLU, but use neutral HID for Histidine. The keywords `sidechain neut all` specifies all the ionized side chains in LYS, ARG, ASP, and GLU to be neutral by deleting H or adding H atoms; keywords `sidechain neut base` specifies the basic ionized sidechains, LYS and ARG, to be neutral; similarly, keywords `sidechain neut acid` specifies ASP and GLU to be neutral. The residue HID (HIS with H atom at delta position) can be substituted to HIP (protonated HIS) or HIE (HIS with H at epsilon position) by the keyword `substitute`, which is described next. Alternatively, neutral sidechains can be specified by giving LYN, ARN, ASH, or GLH as residue codes in the residue list or input PDB file, and specific forms for HIS can be specified as HID (default), HIE, or HIP.

The keyword `substitute` allows one to modify the primary sequence (most useful if the sequence is obtained from a PDB file) and it *must* appear after the list of residues or PDB file; otherwise Impact will have trouble figuring out what to substitute. In this context *resn1* and *resn2* refer to the names of the residues, as in '`ala`', and *rnumber*, as always, to the number of the residue that must be replaced. If *rnumber* is omitted, ALL residues of name *resn1* are changed to *resn2*. For example,

```
build primary name peptide2 type protein -
   ala gly ser leu *** ser ser ala end -
   chainname a chainname b -
   substitute ala to gly rnumber 1
```

is equivalent to

```
build primary name peptide2 type protein -
   gly gly ser leu *** ser ser ala end -
   chainname a chainname b
```

After the primary structure has been built, crosslinking between any two residues can be specified. This option should be used **only** if the `automatic` keyword (see Section 2.2.1.7 [Crosslink (build)], page 27) is given later. The decision whether to build a crosslink or not is taken by checking whether the distance between the specified atoms (in all

[4] Chain names must be one character long, as in the standard PDB format.

residues with the given name, e.g., all `ala` residues) is smaller than *cutoff_distance*. The atomic coordinates are read from the PDB file *fname*, which should therefore have been specified either on the same line or in a previous '`build primary`' line. Failure to do this will result in unpredictable results. To force a crosslink between specific residues (see Section 2.2.1.7 [Crosslink (build)], page 27). *Caution:* If only disulfide bonds are desired the `rname` and `aname` parameters need not be specified. The default cutoff distance is 2.2 Å.

It should be noted that `resn` (or `resnumber` or `rnumber`) residue numbers supplied in the main input file have the following meanings: positive numbers mean the residue numbering used in the original PDB file; negative numbers mean the reordered Impact residue numbers (i.e., sequential, starting with 1); 0 means all applicable residues.

2.2.1.3 Primary type DNA/RNA

- `build primary name` *spec* `type [ DNA | DNAB | DNAA | DNAZ | RNA ] -`
  `[` *base_list* `end] [ read file` *fname* `] -`
  `(chainname` *chain_name* `)` repeat for all chains `-`
  `[ [ substitute` *resn1* `to` *resn2* `[ rnumber` *resn* `] ] ]* -`
  `[ crosslink name` *spec* `[ file` *fname* `] -`
  `[ rname` *resna* `aname` *atna* `rname` *resna* `aname` *atna* `]+ -`
  `[ cut` *cutoff_distance* `] ]`
  `[ nopom ] [ print ]`

  DNA and RNA molecules can also be constructed, using D or R-nucleotides. This option is currently valid only for the `AMBER` force field, it will be extended to include the OPLS force field. Note that `DNA` and `DNAB` are equivalent since this is the most common form.

  The coordinate information is stored in the residue database in the form of internal coordinates based on the B-DNA structure presented by Arnott & Hukins, *Biochemical and Biophysical Communications*, **47** (1972). In order to build A-DNA, angle and dihedral internal coordinates are replaced by those of A-DNA. These internal coordinates of A-DNA were also obtained from the Arnott paper. In order to build Z-DNA, angle and dihedral internal coordinates are replaced by those of Z-DNA. The internal coordinates of Z-DNA were obtained from Rich & Wang, *Science*, **211**, (1981).

  An important aspect of the DNA built by Impact is that hydrogen atoms are explicitly defined in the molecule. (**Caution:** Since the hydrogen atoms are explicitly defined, the resulting structures are quite large.)

  The standard DNA molecule is built in the $5' \rightarrow 3'$ direction Each strand *must* be given in this direction. The program will not work correctly for mismatched base pairs, or for DNA that is not specified as shown below.

The B-DNA molecule is similar to the Watson-Crick double helix. This helix is right-handed. The A-DNA molecule is also right handed, but repeating units have a 3′-endo sugar pucker as opposed to the C2′-endo sugar pucker in B-DNA. Z-DNA is a left-handed helix containing only guanine and cytosine bases where cytosine has a C2′-endo sugar pucker and guanine has a C2′-exo to C1′-exo sugar pucker.
The *base_list* for DNA **must** be of the form

```
[ ohb ]  list of bases [ he ] *** -
    [ ohb ] list of complementary bases [ he ]
```

where `ohb` represents the starting OH group before the phosphate and `he` represents the final capping hydrogen. (Analogously, `ohe` represents the final capping OH group for a terminal phosphate, and `hb` is the capping hydrogen of a base at the beginning of a sequence.) The bases should be selected from `ade`, `thy`, `gua`, `cyt` or `pom` (see below). The keyword `nopom` removes the phosphates from each DNA base. They can be added as separate residues by adding `pom` between residue names. This may be necessary for reading `AMBER` coordinate files. The default phosphate groups are added to each DNA nucleotide—thus the phosphate and the base have the same residue number. This is necessary for reading most PDB files.

2.2.1.4 Primary type Ligand

- `build primary name` *spec* `type ligand [ mole` *mname* `] -`
  `[ read file` *pdb_filename* `|` *residue_list* `end]`

This is the command to define a molecular species of type `ligand` (can be used for any organic molecule in any context).

Caution: The species type `ligand` is deprecated in favor of `type auto` (see Section 2.2.1.5 [Auto (primary type)], page 24) and may disappear in future releases. The residue template file generation feature of the `build primary type ligand` command is also deprecated in favor of the more general `write template` command (see Section 3.1.7 [Read/write (minimize)], page 74). Both of these commands are only compatible with `set ffield amber86` and `set ffield opls` (see Section 2.1.2 [Set ffield], page 17).

The option `type ligand` is generally used to generate a template file from a PDB file specified by the command option '`read file`' *pdb_filename*. Impact template files (see Appendix A [Impact Files], page 221) contain all of the geometrical, topological and energetic information of the molecule. They are used to build macromolecules (see Section 2.2.1.1 [Primary (build)], page 20) and can be modified to achieve direct control over the molecular structure. The command option *residue_list* `end` instead is generally used when a template file was generated from a previous run and the user found it necessary to

manually modify it to suite some special need (such as when an unusual chemical group in not properly recognized by the automatic atom typing code).

The `read file` *pdb_file* option builds a template from the PDB file, and the *residue_list* `end` option is used when the template file is made available from previous runs (usually for manual editing). The first option is the most common; it reads in a PDB file and uses the first part of the file name as the residue name. For example, if the PDB file has a name '`drug1.pdb`', the template file will be named '`drug1`'. The program will assign the OPLS-AA atom-types (the AMBER force field is not supported for the type `ligand`) for each atom in the ligand molecule, and find parameters for bonds, angles, proper torsions and improper torsions. All the information will be organized in a template file using the same format as in a protein or DNA residue, as described in Appendix A [Impact Files], page 221. The template files are free formatted for reading.

Because no more than two species can be simultaneously defined, it may be necessary to put multiple molecules in one species. This can be done, for example, as follows:

```
create
  build primary name 1stp type protein mole prot read file 1stp.pdb
  build primary name drug type ligand mole liga read file liga.pdb
  build primary name drug type ligand mole ligb read file ligb.pdb
  read coordinates name 1stp mole prot brookhaven file 1stp.pdb
  read coordinates name drug mole liga brookhaven file liga.pdb
  read coordinates name drug mole ligb brookhaven file liga.pdb
quit
```

Here a protein is entered as species `1stp` and two ligands are entered into the single species `drug`. Note the extra syntax `mole` is needed in this case specifying the molecule names, both in the build and read sections. In general, for inputs involving multiple molecules, the `mole name` syntax is required any place where `name` *species-name* is used. Note that an explicit solvent species must be treated as a unique species and that other molecule types can not be added into the solvent species. The specification of the solvent species thus does not provide for a `mole` syntax.

2.2.1.5 Primary type Auto

- `build primary type auto name` *spec* `-`
  `[mole` *molname*`] [check] -`
  `[ gotostruct` *structnum* `| nextstruct ] -`

```
read [ maestro | pdb | sd ] file filename -
[tagged tagname] [ cmae ] [ fos | fobo ]
[notestff|notest]
```

The '`type auto`' option of the '`build primary`' command is generally used to interface Impact to the Maestro graphical front end. An Impact species of type '`auto`' contains internally all of the information necessary to produce a molecular file in Maestro format that can later loaded into the Maestro graphical front end. If the species is constructed using exclusively files in Maestro format it is ensured that graphical and other information originally contained in the input Maestro files is carried over to the Maestro file in output (see Section 3.1.7 [Read/write (minimize)], page 74). See Section C.1.8 [Simulation from Maestro file (m2io)], page 246 for an example. The '`build primary type auto`' command also supports input from PDB and SD files; in these cases Impact essentially converts these formats to Maestro format internally.

`name` Specifies the identifier *spec* of the species to be created or the of the existing species to which a new molecule is to be added.

`mole` Specifies the identifier *molname* of the molecule to be created.

`check` Instructs Impact to compare the molecular structures of the molecules currently loaded in the species with the ones being loaded. If the two sets are considered chemically identical, except perhaps for a conformational difference, the automatic atom typing of the molecules are not performed even if the `build types` (see Section 2.2.1.11 [Types (build)], page 30) is subsequently invoked. Otherwise all the molecules present in the species are deleted and replaced with the molecule being loaded and the '`build types`' will preserve its normal behavior.

The `check` keyword is necessary after the first structure when reading multiple structures sequentially into the same Impact species. Without it, the atoms of the new structure are appended to those already in the species, rather than replacing them. When reading multiple structures in a `while-endwhile` loop (see Section 5.3.1.1 [while (control)], page 199), the first `build primary` command must occur before entering the loop, without the `check` keyword, whereas the `build primary` command inside the loop must be `build primary check`. Such loops are standard procedure in the Glide docking module (see Section 3.6 [Docking], page 98).

`maestro` Specifies that the molecular file in input is in Maestro format (usually denoted by a `.mae` file extension). The '`tagged`' option is used to specify that only the subset of the atoms tagged with the specified tag *tagname* are to be loaded. Sets of atoms are

sometimes tagged by the Maestro front end to identify special structures of the system (such as the ligand in a ligand-receptor complex, often tagged `LIG_`) in order to instruct Impact to handle them in special ways (such as loading the ligand in a different Impact species from the receptor).

`tagged` An option used with files in Maestro format. See note above.

`pdb` Specifies that the molecular file in input is in PDB format (usually denoted by a `.pdb` file extension).

`sd` Specifies that the molecular file in input is in `MOL` format (usually denoted by a `.mol` or `.sdf` file extension).

`gotostruct`
`nextstruct`
Used for multi-structure files, files that contain a sequence of structures rather than a single structure. '`gotostruct`' instructs to read the structure at the position *structnum* in the file. '`nextstruct`' reads the next available structure in the file starting from the last accessed position (or the first structure if the file has been accessed for the first time). The default is to read the current structure (the first structure or the last accessed structure). Note that Impact maintains only a record of the position of the current open file, so that if *file1* and then *file2* are accessed in sequence, the position information of *file1* is lost.

`cmae` Read partial charges for all atoms from Maestro files. These override charges that OPLS-AA would assign.

`fos` Use formal charges from Maestro or SD files for single atoms. This allows you to choose specific oxidation states for ions, e.g., Fe3+ instead of OPLS-AA's default for Iron, Fe2+.

`fobo` Use all formal charges and bond orders from the input Maestro or SD file, overriding the assignments that the OPLS-AA typer would make.

`notestff` The default behavior of `build primary auto` is to check the lewis structure of the species and skip further processing of structures for which no valid lewis structure could be generated. The '`notestff`' keyword allows processing of the species regardless of the validity of its lewis structure. For additional information regarding lewis structure checking see the '`lewis`' or '`ifo`' keywords.

The keyword is applied to all species that undergo a `build types` command until the next `build primary auto` command

where the default behavior is reverted to unless another '`notestff`' command is given.

2.2.1.6 Primary type Ions

- `build primary ions name` *spec* `-`
  `type [ protein | other | DNA | DNAB | DNAA | DNAZ | RNA ] -`
  resname numbers `[xyz x` *val* `y` *val* `z` *val*`]+ end`

Appends a total number of *numbers* "ions" (any entity, really) to *spec*. The "ions" consist of the single residue *resname*, which should be either present in the residue data base or have been previously constructed with '`build newresidue`' (see Section 2.2.1.8 [Newresidue (build)], page 27). These "ions" will not be part of any chain, i.e., they are not covalently bonded to any of the atoms specified when the primary structure for *spec* was built (which should, of course, occur before '`build ions`' is invoked). For single atom ions, such as Na+, Cl-, Zn2+, etc, the coordinates can be read in here (recommended in fact) through the optional `xyz` keyword. The coordinates of ions can also be read in through subtask '`Read xyz`' Section 2.2.4 [Read (create)], page 34. It should be noted that Impact will not read in metal ion coordinates directly from PDB files.

2.2.1.7 Crosslink

This option inserts connectivity information due to the inclusion of crosslinks into the appropriate structural arrays. For `cys` crosslinks, it is recommended that the residue `cyx` be used in '`build primary`'.

- `build crosslink automatic`

Caution: this *must* be used only if `crosslink` was specified in the '`build primary`' line for at least one of the species and it should always be after all the species have been built. It uses structural information gathered by '`build primary ... crosslink`' to make new bonds between crosslinked atoms (see Section 2.2.1.1 [Primary (build)], page 20).

- `build crosslink name` *spec* `-`
  `[ resnumber` *resn* `atname` *atna* `-`
  `resnumber` *resn* `atname` *atna* `]+`

This option should be used to force crosslinks between residues. **Caution:** '`build primary crosslink`' should *not* be used in this case.

2.2.1.8 Newresidue

- `build newresidue [` *spec* `file` *fname* `]+`

```
build newresidue drug1 file drug1.pdb
build newresidue drug2 file drug2
```

Adds a residue to the data base. Two options can be used, a PDB formatted file with a `.pdb` file name extension (the program will automatically build all internal coordinates, and atom types), or a template file with a name other than one for a PDB file name.

Template file: the file *fname* should contain connectivity information and internal coordinates for the species.[5] Default internal cartesian coordinate must be defined by using equilibrium bond lengths and angles. The information is read from a formatted file. Please see Appendix A for information pertinent to building a residue file. When using a user defined residue, '`build newresidue`' must be called before using the residue in '`build primary`'.

PDB file: this option builds the template from the PDB file. It uses the first part of the file name as the residue name, for example, if the PDB file has a name '`drug1.pdb`', the template file will be named '`drug1`'. The program will assign the OPLS-AA atom types (AMBER atom types are not supported) for each atom in the molecule, and find bonds, angles, proper torsions and improper torsions. All the information will be organized in the template file using the same format as in a protein or DNA residue. As of this writing, the molecule cannot contain more than 1000 atoms, but this limit will be relaxed in future versions.

2.2.1.9 Secondary

'`Build secondary`' is used to build secondary structure into the molecule by changing the value of its torsion angles to the ideal values for that secondary structure. Non-standard secondary structure may also be incorporated with this option. The secondary structure of each species must be built separately.

- `build secondary name` *spec* `fresidue` *first* `lresidue` *last* `-`
  `[ calpha | helix | lhelix | sheet | random [ seed` *num* `] | -`
  `user phi` *phi* `psi` *psi* `| -`
  `turn type [ i | ip | ii | iip ] | -`
  `sidechain [ resnumber` *resn* `] -`
  `chi` *ichi* `[ torsion` *chi* `| seed` *num* `|` nil `] ]`

Builds the secondary structure of a protein.[6] The parameters *first* and *last* specify the numbers of the first and last, respectively, residues that are involved in the secondary structure in question. The keywords that specify the secondary structure have the following meanings:

[5] There is a small limit, typically 10, in the number of new residues that the program can handle.

[6] Normally one obtains the secondary structure from a PDB file, but this option allows the user to change it if so desired.

`random` Specifies a random coil structure (or lack of). The torsional angles will be taken from a random number generator that is initialized with the parameter to `seed` (the default value is 111).

`calpha` Uses just the C_α coordinates to obtain other backbone coordinates.

`helix` Specifies a α-helical structure. The angles ψ and ϕ are both set to -60.

`lhelix` Specifies a left-handed helix. The angles ψ and ϕ are both set to 60.

`sheet` Specifies a β-sheet. The angle ψ is set to 135 and ϕ to 220.

`user` The angles ψ and ϕ are set to the specified values.

`turn` Changes ψ and ϕ according to the type of turn. The types of turns are shown below.

`i` β_i turn, where $\phi = -60.0$ and $\psi = -30.0$ for first residue, and $\phi = -90.0$ and $\psi = 0.0$ for second residue.

`ip` β_i' turn, where $\phi = 60.0$ and $\psi = 30.0$ for first residue, and $\phi = 90.0$ and $\psi = 0.0$ for second residue.

`ii` β_{ii} turn where $\phi = -60.0$ and $\psi = 120.0$ for first residue, and $\phi = 80.0$ and $\psi = 0.0$ for the second residue.

`iip` β_{ii}' turn where $\phi = 60.0$ and $\psi = -120.0$ for first residue, and $\phi = -80.0$ and $\psi = 0.0$ for second residue.

`sidechain`
The parameter *chi* (selected at random if not specified, in which case `seed` has the same significance as for `random`) gives the new value of the specified torsion angle. The parameter *ichi* selects which side chain torsion to modify.

• `build secondary name` *spec* `[ ADNA | BDNA | ZDNA ]`

Builds the secondary structure of a DNA molecule (this must be specified after '`build primary`'). Of course, *spec* should have been built with the corresponding primary structure. Impact will take the strands

that were specified and put them into their double helical form by performing Eulerian angle transformations on the strands built by Impact. For B- and A-DNA, the Euler angles used are based on the relationship the strands have in the S. Arnott paper whereas in Z-DNA it is based on the relationship the strands have in the A. Rich paper.

2.2.1.10 Solvent

Impact distinguishes between species that are used primarily as *solvent* and those that are used as *solute*. This option should be used in the place of '`build primary`' to specify the nature of the solvent.[7] A typical although simplified use is given in the following example:

```
CREATE
   build primary name dipep type protein ala gly end
   build solvent name agua type spc nmol 216 h2o
QUIT
```

If both solvent and solute are present, then Impact will automatically remove those solvent molecules that overlap the solute. The removal algorithm is based on safe default settings which however may cause the removal of too many solvent molecules, giving a total system density that is too low. These settings can be modified using the `mixture` subtask of the `setmodel` task (see Section 2.3.6 [Mixture (setmodel)], page 52).

- `build solvent name` *spec* `type [ spc | tips | tip4p ] nmol` *num* `h2o`

- `build solvent name` *spec* `type other -`
  `nmol` *num resname* `[ read file` *pdbfname* `]`

Builds the structural arrays for the solvent species *spec*. The first form is used most often since it creates a solvent composed of 'water' molecules. At present it can handle SPC, TIP3P and TIP4P water models. If *type* is not `spc`, `tips` or `tip4p` the user should specify a valid residue name *resname*, i.e., one that either exists in the database or has been specified in a previous call to '`build newresidue`'. The parameter to `nmol` gives the initial number of molecules (which might be different from the final value (see Section 2.3.6 [Mixture (setmodel)], page 52), unless a PDB file name is given, in which case the initial number of molecules will be the larger of *num* and the number of molecules in *pdbfname*.

2.2.1.11 Types

- `build types name` *spec* `[pparam] [lewis` *int*`|ifo` *int*`] -`
  `[patype` *int*`] [plewis` *int*`]`

[7] There can be only one solvent species in Impact.

Assigns OPLS-AA atom types to species *spec*.

Most, but not all, of the Impact tasks require the ability to calculate the energy of the system using a force field. A force field is based on the assignment of an atom type to each atom. When a species is built using type '`other`', '`protein`' or the nucleic acid types, or when using the '`build solvent`' command, the atom type information is contained in the residue template files. Impact also provides a facility to automatically assign `OPLS-AA` atom types to a molecular system and to automatically recognize which bonds, bond angles and torsions are to be included in the energy calculation. This facility is implicitly invoked when building a species using type '`ligand`' in order to generate the corresponding template file. A species built using type '`auto`', however, requires the explicit invocation of the '`build types`' command in order to assign valid `OPLS-AA` atom types.

The '`build types`' command can be invoked for any species (with the exception of solvent species) not just for species of type '`auto`'. For example the invocation of the '`build types`' for a species of type '`protein`' will assign `OPLS-AA` atom types to the protein atoms overriding the atom type information contained in the built-in aminoacid template files. It is actually recommended to do so to ensure atom type consistency between, say, the same protein built using either type '`protein`' and type '`auto`' followed by the '`build types`' command. Although every effort is made to keep the built-in residue template files synchronized with OPLS-AA implementation revisions, it is possible that slight differences may arise at times between the atom types assignments in the residue template files and the atom types assignments produced by the '`build types`' command.

The automatic atomtyping procedure is time consuming especially for large molecules. For time-critical applications involving the energetic analysis of a large number of standard protein structures, for example, consider building the proteins using type '`protein`', which does not require automatic atomtyping. For species built stepwise from individual molecules invoke the '`build types`' command only when the species is completed rather than after each build command. For example the sequence of commands

```
CREATE
  build primary type auto name complex mole receptor -
    read maestro file receptor.mae
  build types name complex
  build primary type auto name complex mole ligand -
    read maestro file ligand.mae
  build types name complex
QUIT
```

and

```
CREATE
  build primary type auto name complex mole receptor -
    read maestro file receptor.mae
```

```
  build primary type auto name complex mole ligand -
    read maestro file ligand.mae
  build types name complex
QUIT
```

will generate identical molecular systems with identical OPLS-AA atom types assignment, but the latter will execute in less time.

The lewis structures of all species to be typed are, by default, checked prior to the assignment of atomtypes and force field parameters. If the species is found to have a valid lewis structure, the species is passed to the automatic atomtyping routine. If the lewis structure is found to be invalid, the lewis structure refinement process is initiated and an attempt is made to generate a valid lewis structure. If no valid lewis structure is generated, further processing on the species is halted unless the '`notestff`' flag is employed in the '`build primary auto`' command. The behavior of the lewis structure checking/refinement process is controlled via the '`lewis`' or '`ifo`' arguments as shown below.

'`lewis 1`' - Use formal charges for isolated atoms from the input structure. Equivalent to setting the '`fos`' flag for a '`build primary auto`' command.

'`lewis 2`' - Use formal charges and bond orders from the input structure. No lewis structure check is performed. Equivalent to setting the '`fobo`' flag for a '`build primary auto`' command.

'`lewis 5`' - Default behavior. First test if input structure is valid, if not then attempt to generate a valid lewis structure.

To print the atom types and force field parameters assigned, add the `pparam` flag to the '`build types`' command. For more verbose printing from the automatic atomtyping process, use the `patype` flag with increasing verbiage in going from values of 1 to 6. For more verbose printing from the lewis structure checking/refinement process, use the `plewis` flag which will output increasing verbosity in going from values of 1 to 6.

2.2.2 Subtask Delete

To build acylated ligands it is necessary to delete the H atom on the residue connected to the ligand. In addition the ligand should be represented as it appears in the acylated form. For example, to delete the H atom of residue number 70, with the H atom attached to heavy atom name OG and the H atom name is HG, the following syntax is used;

```
delete name prot mole pro resnumber  70 atname OG hatname HG
```

This line appears in the CREATE section after the system has been specified with `build`.

2.2.3 Subtask Print

Writes information to the main output file in human-readable form about the structural arrays of a given species.

- `print tree name` *spec*

  Prints out the tree structure for each residue as *natom()*, *join(i)*, *igraph(i)*, *isymbl(i)*, *itree(i)*, *bond(i)*, *angl(i)*, *tor(i)*, *charg(i)*, and *irotat(i)*. The tree has the following structure:

  natom(i) The atom number of atom i.

  join(i) The atom to which atom i is bonded in the tree structure, viewed back down the chain toward the first atom.

  igraph(i) Graph name of atom i, atom name unique to residue.

  isymbl(i) Atom type of atom i.

  itree(i) The tree type of atom i is one of the following.

  `M` ⇒ Main

  `S` ⇒ Side chain

  `E` ⇒ End

  `B` ⇒ Branch

  `3` ⇒ Three way branch

  bond(i) Bond Length between i and *join(i)*.

  angl(i) Angle Between *i-j-k* where

  j = *join(i)*

  k = *join(j)*

  torsion(i) Torsion angle between *i-j-k-l* where

  j = *join(i)*

  k = *join(j)*

  l = *join(k)*

  charg(i) Charge on atom i.

  irotat(i) Last atom affected by a rotation of atom i about the bond to *join(i)*.

- `print structure name` *spec* `[ bond | angle | torsion | excluded ]`

  Prints out structural arrays, i.e., a list of all bonded pairs, angle triplets or dihedral quartets. It can also print the list of excluded atoms for the given species.

- `print ic name` *spec* `[ bond | angle | torsion ]`

Prints structural arrays and corresponding internal coordinate value. All internal coordinates of species *spec* will be printed as specified by the keyword. Internal coordinates due to crosslinks are at the end of the internal coordinate array.

- `print coordinates name` *spec* `[ impact | brookhaven |` nil `] -`
  `file` *fname*

  Prints out coordinates in `impact` format or standard Protein Data Bank (PDB) format. The default is the standard format, for which the keyword is `brookhaven` after the former home of the PDB. The `impact` format is very similar to the standard PDB format except for the nomenclature used for hydrogens (see Section 2.2.4.3 [Coordinates (read)], page 36).

2.2.4 Subtask Read

This subtask reads in additional information needed to define the structure of molecules more precisely. This information includes new coordinates, or residue topology information.

2.2.4.1 Xyz

- `read xyz name` *spec* `resnumber` *resn* `atomname` *atna* `-`
  `x` *real* `y` *real* `z` *real*

  Changes the cartesian coordinates (x, y, z) of the specified atom to the input values. This option is mainly used to change a few coordinate values, as otherwise it is more convenient to read the coordinates from a file (see Section 2.2.4.3 [Coordinates (read)], page 36).

2.2.4.2 Internal

This option allows the user to change the internal coordinates of a molecule after it has been built (see Section 2.2.1.1 [Primary (build)], page 20). Care must be taken, though, to specify the atoms in the correct order (this is a limitation in Impact that might not be removed in the near future). The best way to ensure the ordering is to issue a '`print tree`' command in a previous run and to use the structural information obtained from the second column in the display of each residue. Let us clarify this with an example. If a system is created with the commands

```
CREATE
   build primary name pep1 type protein ala gly ala end
   print tree name pep1
QUIT
```

then the (main) output file will contain the following fragment, showing the structure of the first residue, `ala`:

```
Residue   1 =  ALA            residue total =    1


     Bond array begins with     1    1st atom in residue =    1

 1    0   N     N   M         0.000000    0.000000    0.000000    -0.463    27
 2    1   HN    H   E         1.010000    0.000000    0.000000     0.252     2
 3    1   CA    CT  M         1.449000    0.000000    0.000000     0.035    27
 4    3   HA    HC  E         1.090000  109.500000    0.000000     0.048     4
 5    3   CB    CT  3         1.525000  111.100000    0.000000    -0.098     8
 6    5   HB1   HC  E         1.090000  109.500000   60.000000     0.038     6
 7    5   HB2   HC  E         1.090000  109.500000  180.000000     0.038     7
 8    5   HB3   HC  E         1.090000  109.500000  300.000000     0.038     8
 9    3   C     C   M         1.522000  111.100000    0.000000     0.616    27
10    9   O     O   E         1.229000  120.500000    0.000000    -0.504    10
```

Given this structure the following command will fail:

```
CREATE
  read internal name pep1 bond -
    resnumber 1 atomname N resnumber 1 atomname CA bond 1.23
QUIT
```

but this one will succeed:

```
CREATE
  read internal name pep1 bond -
    resnumber 1 atomname CA resnumber 1 atomname N bond 1.23
QUIT
```

The first command fails because the second column of the row that corresponds to atom `N` has a zero, whereas the second column of atom `CA` has a one (it is bonded to `N`) and the second command succeeds.

Caveat: '`read internal`' *cannot* create new internal coordinates, i.e., a new structure. It can only modify the values of preexisting internal coordinates that are defined in the residue databases (or constructed when two residues are joined together).

- `read internal name` *spec* `bond -`
  `resnumber` *resn* `atomname` *atna* `-`
  `resnumber` *resn* `atomname` *atna* `-`
  `bond` *value*

  Changes the internal bond length between the two specified atoms.

- `read internal name` *spec* `angle -`
  `resnumber` *resn* `atomname` *atna* `-`
  `resnumber` *resn* `atomname` *atna* `-`

`resnumber` *resn* `atomname` *atna* -
`angle` *value*

Changes the internal angle between the three specified atoms.

- `read internal name` *spec* `torsion` -
  `resnumber` *resn* `atomname` *atna* -
  `resnumber` *resn* `atomname` *atna* -
  `resnumber` *resn* `atomname` *atna* -
  `resnumber` *resn* `atomname` *atna* -
  `torsion` *value*

  Changes the internal dihedral angle between the four specified atoms.

2.2.4.3 Coordinates

Reads in coordinates from a standard-format PDB file or an Impact generated coordinate file, changing the value of the internal coordinates that match those read in. If hydrogens (or side chains) are not included in the file, their internal coordinates will be automatically adjusted to reflect the new reference frame wherever possible. The default format is standard PDB file format.

- `read coordinates [ brookhaven | impact ] [ chain ] -`
  `name` *spec* `file` *fname*

  The keyword *chain* forces reading of only one chain.

  The buried or bound waters in PDB files will be read in as default. However, the residue names for these waters must be `HOH` or `SPC`. If they happen to be `UNK` or something else, user needs to convert them to be `HOH` first; otherwise, Impact will just skip them.

  The only difference between `impact` and `brookhaven` formats is that in the latter the atom name is a four letter name (where the first 2 spaces are the atomic symbol and the second two are unique atom codes). In the case of a one letter atomic symbol, a leading blank is added. Thus the α carbon would be called `_CA_`. In `impact` the addition of hydrogens requires the use of all four positions in order to uniquely define the names of all the atoms, we therefore removed all the leading blanks. Thus a δ carbon, and its hydrogens would be called `CD1_` and `CD2_` and HD11 in `impact`, as opposed to `_CD1` `_CD2` and 1HD1 in `brookhaven`.

  It is important to review a PDB file before reading it in directly. Multiple chains contain `TER` cards after each chain, and these must be deleted because this option stops reading when `TER` is reached. Prior to continuing with calculations, for insertion and deletion codes, print out a PDB file after reading it in to see the new numbering scheme. Also, please analyze PDB files for unknown or nonstandard residues.

2.2.4.4 Bound Waters

As mentioned in the above `read coordinates` subsection, the bound waters in PDB files will be read in as default. However, the residue names for these waters must be `HOH` or `SPC`.

The bound waters with residue labels `HOH` or `SPC` in PDB files generally require the H atom coordinates to be defined. Impact simply defines the H atom coordinates for each water O atom by placing one H atom close to a neighboring atom (within a cutoff) and by placing the other H atom so as to maximize its distance from other atoms (at the fixed HOH angle). At present, Impact always regenerates the H-atom coordintes for HOH residues even if they are given in the original file.

If the user does not want to read in bound waters in a PDB file, he/she can turn this option off by the keyword `noboundwater` no matter what the residue names are.

- `read coordinates brookhaven name` *1stp* `file` *1stp.pdb* `noboundwater`

2.3 Task Setmodel

The object of this task is to process energy, structural and simulation parameters required for the following simulations:

- pure solute;
- pure solvent;
- mixed solute-solvent;
- crystal.

This task must be completed before calls to `minimize`, `dynamics`, or subtasks of `analysis` requiring energy evaluations. The use of this task is shown in Section C.2.5 [Protein-water MD (example)], page 260, Section C.2.4 [Protein solvate (example)], page 257, and Section C.2.3 [Protein size (example)], page 253.

2.3.1 Subtask Energy

Read in information needed to calculate force and energy in MM, MD and MC simulations, including boundary conditions, potential cutoff, constraints, and screening of Coulomb interactions. The following options are allowed in subtask `energy`.

2.3.1.1 Periodic

Sets up periodic boundary conditions for species *spec* based on the supplied `bx`, `by`, `bz` box dimensions, which should be in Å. Instead of specifying a species by name you can use the keyword `all`.

- `energy periodic [ name` *spec* `| all ] [ bx` *val* `by` *val* `bz` *val* `]`

2.3.1.2 Molcutoff

Specifies that a molecule-based cutoff should be used for species *spec*. Again, `all` can be used if one wishes to subject all species to molecule-based cutoffs. If instead `none` is given, all species will have atom-based cutoffs (this is the default).

- `energy molcutoff [ all | none | name` *spec* `]`

If a molecular cutoff is not specified for a species then an atom type cutoff is assumed. The term *molecular cutoff* implies that the center of mass of a molecule is used to determine whether a nonbonded pair is to be stored on the nonbonded list. In the actual energy calculation, distances between atom pairs are always used to calculate nonbonded energy terms. For simulations involving water, molecular cutoffs should always be used in order to avoid splitting dipoles in the electrostatic calculations, unless the Fast Multipole Method (FMM) is chosen. Also, when periodic boundary conditions are used, a molecular cutoff should always be used if there is a possibility that

a molecule may drift out of the box (this is likely in the case of water but not of a solute molecule that is much smaller than the box). Again, if the Fast Multipole Method is chosen this option is silently ignored. **Please Note:** Molecular cutoffs are not compatible with the Truncated Newton minimizer at this time (see Section 3.1.3 [Tnewton], page 72).

For sample input files, see also Section C.3.6 [Area vs. Solv Energy (example)], page 304 and Section C.3.4 [MDanalysis (example)], page 284.

2.3.1.3 Constraints

Instruct Impact to read in bonds or distances that should be constrained during molecular dynamics using the `SHAKE` method. There are two ways of specifying constraints:

- `energy constraints read file` *fname*

will read the constraints from the given file (see below for a description of the format of the constraint file). Alternatively,

- `energy constraints [ bond | lonepair ]`

constrains all bonds to their equilibrium values based on the bond parameters read in by `setmodel read`. Therefore, parameters must be read first for this option to work. Note that **all** species will be thus constrained. The keyword `lonepair` is a little more complicated. It finds all atoms whose names have the first two letters LP and adds the bonds and angles associated with them to the `SHAKE` constraints. Lone pairs move too much due to their low atomic weight and therefore this option should be used when the force field is AMBER86 and cysteines and methionines, which contain LP's on the sulfur, are present. The added constraints only apply to bonds made directly to the LP's (such as SG–LP) and the angles involving two LP's (such as LP–SG–LP).

The maximum allowed number of iterations in the `SHAKE/RATTLE` algorithms can be controlled with the keyword `maxiter` (default: 1000)

- `energy constraints maxiter` *num*

2.3.1.4 Constraint file format

1. The file that contains the constrained distances is free format but the following lines are read in:
   - Number of constraints for a species.
   - Pairs of atoms constrained and constrained distance value.
     Caution: it is expected that constraints for all species are in one file and these are added to the list for the species, e.g.,

     ```
     energy constraints bond
     ```

     can be used first followed by

     ```
     energy constraints read file fname
     ```

where *fname* contains only the list of distances needed to constrain angles.

2. Sample constraint files
   - for H_2O constraining OH distances to 1.0 Å and HH distance to 1.633 Å:

```
3
1 2 1.0
1 3 1.633
2 3 1.0
```

   - If species 1 is unconstrained and species 2 is constrained water:

```
0
3
1 2 1.0
1 3 1.633
2 3 1.0
```

Caution: If the option '`energy constraints bond`' is chosen and a constraint file is not read, all bonds in the molecule are constrained to the equilibrium values corresponding to each bond type as listed in the input energy parameter file. This is done using the `SHAKE` algorithm.

2.3.1.5 Parm

Read in parameters such as nonbonded cutoffs and nonbonded list update frequency, which are used by several energy manipulation tasks such as `dynamics`, `minimize`, `montecarlo`, `tormap`, and `potfield`.

- `energy parm [ cutoff | hbcutoff ]` *value*

Sets a given cutoff distance to the length specified in *value*, which should be in Å. The keyword `cutoff` selects the nonbonded cutoff, which is used for both the Lennard-Jones and the electrostatic interactions (unless the Fast Multipole Method is used). This is a sharp cutoff. `Hbcutoff` selects the cutoff for hydrogen-bond interactions, which defaults to 3.5 Å.

- `energy parm scr14` *value*

Sets the 1–4 nonbonded screening constant (2.0 by default).

- `energy parm [ dielectric` *value* `[ distance | nodistance ] ]`

Sets the value of the dielectric constant (1.0 by default). These options allow the choice of a distance-dependent or a constant dielectric function. One of these must be specified or the program will stop.

- `energy parm listupdate` *num*

Sets the number of steps between updates to the nonbonded (Verlet) list. If `listupdate` is not specified, it defaults to 10.

- `energy parm print` *num*

Sets the frequencies at which the energy terms are printed to the output.

For example input files see Section C.3.6 [Area vs. Solv Energy (example)], page 304 and Section C.3.4 [MDanalysis (example)], page 284.

2.3.2 Subtask Read

This command is used to read in energy parameters from a separate file or from the main input file.

- `read parm [ noprint | minprint | allprint | nil ] file` *fname*

The keyword `noprint` disables printing of the parameters as they are read; `minprint` prints a complete list of the system's parameters, and `allprint` prints an extremely verbose list. In this option, parameters are printed for every bond, angle, torsion, etc. in the file, not just for those parameters required for the system under consideration. The default is `minprint`.

- `read [ char | epsi | hbsc ] [ file` *fname* `]`

Forces reading of charges (`char`), Lennard-Jones ε (`epsi`), or hydrogen-bond (`hbsc`) parameters. These last three options can be followed by a file specification or, in the same input file, a sequence of lines terminated by the keyword `quit` by itself. In any case these lines must match the following pattern:

`residue name` *spec* `resnumber` *num* `atomname` *atom_name new_parameter*

The metavariable *new_parameter* must be one of the following:

`newcharge` *value*	(for `char`)
`newepsilon` *value*	(for `epsi`)
`scale` *value*	(for `hbsc`)

2.3.3 Subtask Print

Write information in user readable form to the main output file or another file specified in the command line.

- `print pdb [ species` *species_number* `] [ impact | brookhaven ] -`
  `file` *fname*
- `print solvent file` *fname*

The keyword `species` lets the user specify which species' coordinates should be printed out. **Warning:** `species` must be followed by a number (from 1 up), not the name of the species.

2.3.4 Subtask Setpotential

Read in information about the chosen potential function. Each option at the outermost level (as `mmechanics`) should be on its own line.

2.3.4.1 Mmechanics

Sets up a standard molecular mechanics potential function taking the following options.

- `mmechanics [ all | name` *spec* `| nil ] -`
  `[ force | noforce | nil ] [ noecons ] -`
  `[tail | notail | nil ] [ nobond ] [ noangle ] [ notors ] [ no14 ] -`
  `[ nohb ] [ novdw ] [ ewald [ kmax` *km* `] [ alpha` *alfa* `] ] -`
  `[ fmm level` *level* `maxpole` *poles* `[ smoothing ] ] -`
  `[ consolv [ pbf | sgb | nil ]` *consolv_options* `] -`
  `[ pff [pffevery` *num*`]]`

`all` Use of `all` flags that the options `nobond`, `noangle` and `notors` refer to all species, otherwise use `species` *spec*.

`force`
`noforce` `Force`/`noforce` determine whether forces should be calculated. Forces are required for `minimization` and `dynamics`. (This is the default.) Currently this option is ignored if the Fast Multipole Method is used.

`noecons` Determines whether NOE (Nuclear Overhauser Effect) constraints will be added to the potential (the default is no NOE constraints).

`tail`
`notail` Determines whether long-range corrections to the van der Waals energies due to cutoffs are made. `Tail` is needed for constant pressure simulations (the default is `notail`).

`nobond` Flag to turn off `bond` stretching term.

`noangle` Flag to turn off valence angle bending term.

`notors` Flag to turn off torsional twisting term.

`no14` Flag to turn off both 1-4 interaction term (`nonb14` and `noel14`).

`noel` Flag to turn off electrostatic term.

`nohb` Flag to turn off hydrogen bond term.

`novdw` Flag to turn off van der Waals (non-bonded) interaction term.

`ewald` Makes Impact use the Ewald summation method to handle the long-range electrostatic interactions. It only works if all species have periodic boundary conditions. To describe the parameters following the keywords `kmax` and `alpha` it is convenient to recall the definition of the Ewald potential (with 'conducting boundary conditions'):

$$\Phi(\mathbf{x}) = \sum_{\mathbf{n}} \frac{\operatorname{erfc}(\alpha\|\mathbf{x}+L\mathbf{n}\|)}{\|\mathbf{x}+L\mathbf{n}\|} + \sum_{\mathbf{k}\neq\mathbf{0}} \frac{4\pi}{L^3\|\mathbf{k}\|^2} \exp\left(-\frac{\|\mathbf{k}\|^2}{4\alpha^2} + i\mathbf{k}\cdot\mathbf{x}\right) - \frac{\pi}{L^3\alpha^2}.$$

This formula represents a solution to the Poisson equation for a unit charge under periodic boundary conditions (there is a negative background that renders the system neutral, as otherwise it can be shown that there is no solution) as a sum of two infinite series, both of which converge exponentially. The first, so-called 'real-space sum', converges faster the larger the value of α is. Conversely, the second sum converges faster the smaller this value. Impact restricts the first sum to the original copy, that is, it only considers the terms with $\mathbf{n} = \mathbf{0}$. The second sum, the 'reciprocal-space sum', is restricted to those values of $\mathbf{k}$ whose components are, in magnitude, less than or equal to the parameter specified by the keyword `kmax` (default: 5). The α parameter has by default the value $5.5/L$, where L is the linear dimension of the box (which must be cubic). The user can change this value, however, with the `alpha` keyword. Note, however, that changing this parameter might require changing the maximum number of reciprocal-space vectors also. A good reference for the Ewald summation method is the book by Allen and Tildesley, *Computer Simulation of Liquids*, Oxford University Press, 1991. For the mathematically inclined we recommend also the article: de Leeuw, Perram and Smith, *Simulation of electrostatic systems in periodic boundary conditions. I. Lattice sums and dielectric constants*, Proc. R. Soc. London, **A373**, 27–56 (1980).

`fmm` Selects the Fast Multipole Method (FMM) for the calculation of the electrostatic interactions. The number following `level` should be the desired number of levels in the hierarchical tree. Since the nodes of the tree correspond to subsequent subdivisions of the simulation box into halves along each direction, if level l is selected, the number of boxes at the lowest level will be 8^l and the linear dimension of each one box at that level will be $L/2^l$ with L being the linear dimension of the simulation box (which must be cubic).

The number following `maxpole` is the maximum number of multipole moments that will be used to approximate the potential and field produced by 'far' clusters. Currently a minimum of four (4) and a maximum of twenty (20) multipoles are allowed. The keyword `smoothing` determines whether a sharp or smooth cutoff are used to separate the direct forces into near and far components. It is only relevant when using the Reversible RESPA integrators (see Section 3.2.2 [Dynamics Subtask Run], page 79) with more than two stages. If periodic boundary conditions are in effect, the potential that gets computed coincides with the Ewald potential (see above), but the algorithm is completely

different. One important restriction when using the FMM with periodic boundary conditions is that the system must be electrically neutral, i.e., the sum of all point charges must be zero. The main reference for the FMM is Greengard's thesis, *The Rapid Evaluation of Potential Fields in Particle Systems*, The MIT Press, Cambridge, 1988. For an example, see Section C.4.1 [FMM (example)], page 316.

Because FMM calculations scale linearly with the total number of atoms, they can provide a significant speed advantage in calculating electrostatic interactions for large systems when it is not desirable to use cutoffs. Systems large enough for FMM to be advantageous may be large macromolecules or complexes of them, or smaller molecules with a large number of explicit solvent molecules. If it is possible to impose periodic boundary conditions, then the Ewald method (which requires such boundary conditions) tends to be faster than FMM for systems containing more than about 20000 atoms.

PLEASE NOTE: The Fast Multipole Method cannot currently be used with the truncated Newton minimization algorithm (`tnewton`) (see Section 3.1.3 [Subtask Tnewton], page 72), or with SGB continuum solvation (see below). It is available with PBF continuum solvation (see below), but the FMM is not applied to the continuum solvent itself. Unless the solute is quite large, therefore, it may not be advantageous to use FMM with continuum solvent.

`consolv [sgb]`

- `mmechanics consolv sgb [ cutoff` *val* `] -`
  `[ nonpolar` *val* `] [ debug` *val* `]`

SGB, the default option for `consolv` is a surface area based version of the Generalized Born model, which can be proved to be a well-defined approximation to the boundary element formulation of the Poisson-Boltzmann (PB) equation[1]. The relationship of the surface area methodology to the volume-integration based approach of the original GB model[2] can be found in Ghosh et al.'s paper. With empirical corrections, SGB produces significant improvements in accuracy, as compared to the uncorrected GB model.

PLEASE NOTE: This solvation method cannot currently be used with the Fast Multipole Method FMM (see above).

[1] A. Ghosh, C. S. Rapp, and R. A. Friesner, *J. Phys. Chem. B*, **102**, *10983*, (1998)
[2] Still, et al. *J. Am. Chem. Soc.*, **112**, *6127*, 1990

`cutoff` The `cutoff` parameter specifies how far any atom must move from the coordinates used in the previous calculation before a new Reaction Field calculation is performed. The default value is 0.1 Å. If all atomic coordinates have moved less than this cutoff, then the previous calculated energy and forces are used for that step in the minimization. A relatively large value of `cutoff` can significantly reduce the required computational time at the expense of some loss in accuracy.

`nonpolar` To use the new *cavity* term (nonpolar energy), you need to set `nonpolar` to 1 in input file, and also set `new_cavity` in '`sgb.param`' (in the data directories listed below) to 1. Currently, the new cavity term is best fit for small molecules; optimizing this term for big systems is under development.

`debug` Setting `debug` to a nonzero value causes diagnostic messages and files to be printed for each calculation.

The `consolv sgb` parameter files are in the directories

```
$SCHRODINGER/impact-v3.0/data/opls
$SCHRODINGER/impact-v3.0/data/opls2000
```

and all start with `sgb`. The files should not need to be modified by the user on an ongoing basis; most useful parameters can be changed via the `sgbp` input file keyword (see Section 2.3.5 [Sgbp (setmodel)], page 50).

If the SGB model is activated, then the following line should appear in the output:

```
%IMPACT-I (mmstd): Using Surface Generalized Born Model
```

In the energy-decomposition printout provided by Impact during the course of a minimization, the continuum-solvent energy is provided under the heading '`RxnFld(Sgb)`'. These energies include the interactions between the atomic-point charges and the induced charges at the solute/solvent interface.

Examples:

- `mmechanics consolv sgb cutoff 0.1`
- `mmechanics consolv sgb nonpolar 1`

`consolv pbf`

- `mmechanics consolv pbf [ pbfevery` *val* `] [ cutoff` *val* `] -`
  `[ rxnf_cutoff` *val* `] [ cavity_cutoff` *val* `] -`
  `[ low_res | med_res | high_res ] [ debug` *val* `]`

PBF is a Poisson-Boltzmann Solver. It takes as input a set of atomic coordinates, their charges and radii, a solvent radius, and dielectric constants for the solute and solvent and computes the electrostatic potential from the resulting Poisson-Boltzmann equation. The reaction-field energy (electrostatic interaction of the fixed atomic charges with the induced surface charges at the solute/solvent interface) and gradient are then calculated. The reaction-field terms effectively represent the average interaction between the solute molecule(s) and the solvent. The advantage of this approach is that the large number of solvent molecules typically used in a solution-phase molecular simulation or minimization are not required, thereby dramatically reducing the computational expense. While treating the solvent as a continuum rather than a collection of discrete molecules is clearly an approximation, it has been shown to be a fairly good one for many types of calculations.

The novel feature of PBF over other algorithms used to solve the Poisson-Boltzmann equation is the use of a finite-element mesh with tetrahedron grids. This approach allows the density of grid points used in solving the discretized equations to be optimized such that accurate results may be achieved with a minimal number of grid points and hence with minimal computational effort. For example, a high density of points is required at the solute/solvent interface to compute a accurate and numerically stable reaction-field gradient. Other approaches using, for instance, a finite-difference method with cubic grids do not have this flexibility and must use a large number of points to obtain comparable accuracy. The use of a finite-element mesh also allows a high density of points to be used in a particular region of interest, e.g., a enzyme-binding site and a lower density of grid points elsewhere in the system, again minimizing the computational effort.

`pbfevery` This parameter sets the frequency in timesteps when a PBF calculation is performed. In between timesteps use the most recent PBF energies and forces.

`cutoff` The `cutoff` parameter specifies how far any atom must move from the coordinates used in the previous calculation before a new Reaction Field calculation is performed. The default value is 0.1 Å. If all atomic coordinates have moved less than this cutoff, then the previous calculated energy and forces are used for that step in the minimization. Preliminary

results suggest that the pbf energy and gradient are slowly varying functions of the atomic coordinates, relative to the other energies and forces involved in a typical molecular mechanics calculation. A relatively large value of `cutoff` can significantly reduce the required computational time at the expense of some loss in accuracy.

`cavity_cutoff`
: The keyword `cavity_cutoff` is used for cavity term recalculation. It is similar to the keyword `cutoff`.

`low_res` Use the low grid point resolution setting. This is the default.

`med_res` Use a medium grid point resolution setting.

`high_res` Use a high grid point resolution setting. This is the most expensive setting, but also the most accurate.

`debug` Setting `debug` to a nonzero value causes diagnostic messages and files to be printed for each calculation.

The `consolv pbf` parameter files are in the directories

```
$SCHRODINGER/impact-v3.0/data/opl
$SCHRODINGER/impact-v3.0/data/opls2000
```

and all start with `pbf`. The files should not need to be modified by the user on an ongoing basis. A few parameters, however, may need to be changed occasionally. For example, the dielectric constants used for the solutes and solvent can be changed in the '`pbf.com`' file. Also the solvent radius can changed by editing the same file.
If the PBF model is activated, then the following line should appear in the output:

```
%IMPACT-I (mmstd): Using Poisson-Boltzmann Model
```

In the energy-decomposition printout provided by Impact during the course of a minimization, the continuum-solvent energy is provided under the heading '`RxnFld(Pbf)`'. These energies include the interactions between the atomic-point charges and the induced charges at the solute/solvent interface.

Because of the large memory requirements for medium-sized and larger proteins, PBF currently writes some arrays to disk and then reads them back in as needed. Currently only one file is being written to disk, '`zzZ_Ctbl_Pbf_Zzz`'. Every effort is made to remove this file after a calculation has completed. However,

if a calculation is aborted or something goes amiss, this file may be left on the disk.
Examples:

- `mmechanics consolv pbf cutoff 0.1`
- `mmechanics consolv pbf low_res cutoff 0.1 cavity_cutoff 0.9`

`pff` This keyword `pff` activates the Polarizable Force Field (PFF). For more information on the theory, see Section 1.7.3 [PFF (ffield)], page 14. In order to use the PFF, you must also specify `SET FFIELD OPLS_PFF_2000` or `OPLS_PFF_2003` (see Section 2.1.2 [Ffield (set)], page 17).

The PFF module is only available under special license from Schrödinger.

The corresponding parameter file to be read in must be '`parampff.dat`' in the `read parm` subtask. Here is one example of how to turn on PFF:

```
SETMODEL
  setpotential
    mmechanics pff [pffevery num]
  quit
  read parm file parampff.dat noprint
  energy parm cutoff 100.0 listupdate 10 diel 1.0 nodist
QUIT
```

The `pffevery` keyword and value are relevant only if `consolv pbf` is also in effect. That is, in a gas-phase simulation with PFF, the `pffevery` value is ignored. With PBF continuum solvation, `pffevery` controls how often (every *num*th simulation step) the polarizable dipoles are updated. The default is `pffevery 0`, which leaves updating under the control of the PFF algorithm.

2.3.4.2 Type

Read the type of potential from the command line. Currently only the keywords `harmonic` and `morse` (for harmonic and morse potentials) are implemented for bonds, and this choice is only available for the AMBER86 force field. With OPLS, bonds are always harmonic.

- `type intramolecular name` *spec* `-`
  `bond [ morse | harmonic ]`

2.3.4.3 Weight

Change the weights of terms in the potential function. Unless otherwise indicated below, the weights are all initialized to 1.0 when `mmechanics` is used.

Caution: Despite the terminology below, intramolecular nonbond terms are affected both by intramolecular and intermolecular electrostatic and LJ weights. The total nonbond weight is the product of the intramolecular (within one species) and intermolecular (between species) weights.

- `weight intramolecular name` *spec* `-`
  `[ bond | angle | el14 | lj14 | elin | ljin | hbin ]` *weight*

The `intramolecular` keyword is used to change the weights of intramolecular terms (those within a single species). The `elin`, `ljin`, and `hbin` keywords change the weights for all included nonbond pairs within the molecule; `el14` and `lj14` change them only for "1-4" pairs, i.e., atoms at the outer ends of a quartet that defines a torsion angle. `hbin` is only used with the AMBER86 force field.

- `weight intermolecular -`
  `[ vdw | eel | hbond | hbelectrostatics ]` *weight*

The `intermolecular` keyword is used to change the weights of intermolecular terms within or between species, thus there is no `name spec` designation. `hbond` and `hbelectrostatics` are only used with the AMBER86 force field.

- `weight constraints name` *spec* `-`
  `[ noe | torsion | hbond ]` *weight*
- `weight constraints buffer` *weight*

The `constraints` keyword defines the weights of various restraint force constants terms. The `noe`, `torsion`, and `hbond` terms are zero by default and define NOE distance and torsion restraint weights, while the `buffer` term is applied to all "buffered" atoms specified via `zonecons` commands. See Section 2.3.9 [Zonecons (setmodel)], page 54. The default `buffer` is 25 kcal/(Å^2 mol).

Caution: `buffer` is not a per-species parameter, but is applied to all buffered atoms in the system.

2.3.4.4 Constraints

Read in distance and torsional constraint lists from a file or the main input file.

- `constraints name` *spec* `noec distance -`
  `con1` *num* `con2` *num* `-`
  `[ file` *fname* `]`
- `constraints name` *spec* `noec torsion -`
  `nsec` *num_sections* `-`
  `( fres` *num* `lres` *num* `tpsi` *value* `-`
  `tphi` *value* `range` *value* `)` repeated *num_sections* times

`distance` signals that distance constraints will be read in.

`torsion` signals that torsion constraints will be read in.

`file` name of constraint file (if different from main input file). This file has the following 6 or 7 fields—in order but free format: (the individual NOE weight is optional see Notes below)
`resn atna resn atna` *lower_bound upper_bound noe_weight*

`con1` number of H-H distance constraints, type 1, to read in.

`con2` number of distance constraints between heavy atoms, type 2, to read in.

If `prochiral` assignments **can** be made and you **know** the constraint is between HB1-HG2 then the atoms names should be specified as such and no averaging over equivalent hydrogens will be implemented.

If `prochiral` assignments can `not` be made (or in the case of equivalent H atoms on methyl groups) you need to specify only the character part of the atom name. In this case averaging over equivalent hydrogens is automatically implemented, ie., for a methylene proton-methyl group interaction.

1. HB1-HG will result in no averaging on the methylene but the methyl group will be averaged
2. HB-HG will result in averaging over the protons in the methylene group `and` the protons in the methyl group.

Number of sections of torsions to be constrained.

`tphi` Target value for ϕ angles (for constraining protein secondary structure).

`tpsi` Target value for ψ values (for constraining protein secondary structure).

`range` Allowed range (i.e., constraint will be `tphi` $\pm$ `rang`).

`ncon` Number of constraints to be read explicitly.

These keywords are read in free format *nsec* times 4(res. no., atom name) target value, range. **Caution:** The weight for the individual NOE constraint is multiplied by the weight for the entire NOE term. It is one by default and can be set to any arbitrary value except zero.

2.3.5 Subtask Sgbp

This keyword sets various SGB continuum solvent simulation parameters. It has no effect unless `mmechanics consolv sgb` is used in a preceding `setpotential` subtask to activate the SGB method.

- `sgbp grid_size` *max* `dock_grid_size` *glide_max* -
  `min_grid_size` *min* `printe [0|1] printf [0|1] -`
  `optimized_rxf_radii [0|1] nonpolar [0|1] active_reg_incr` *val* -
  `buffer_reg_size` *val* `accuracy` *val* `dielectric_in` *epsin* -
  `dielectric_out` *epsout* `hydrogen_radius` *val*

`grid_size`
: The maximum number of grid points each atom can have. The default value is 70.

`dock_grid_size`
: In a Glide calculation, the maximum number of grid points each atom can have, the default is 30.

`min_grid_size`
: The minimum number of grid points each atom can have. The default value is 20.

`printe`
: If set to 1, print the SGB energy. The default is 0.

`printf`
: If set to 1, print the SGB forces. The default is 0.

`optimized_rxf_radii`
: If set to 1 the SGB/NP method[3] optimized reaction field atomic radii are used. The default is 0. The full SGB/NP solvation model is selected when the `nonpolar` option is turned on as well. See below.

`nonpolar`
: If set to 1, the SGB/NP non-polar solvation model is used. See also the `optimized_rxf_radii` above.

`active_reg_incr`
: When setting up the active region region, this amount is added to it. The default is 0.

`buffer_reg_size`
: This defines the buffer region size; the buffer region is located between the active region and the frozen region.

`accuracy`
: The threshhold value used with the `singlelong` multiple time scale scheme, and is related to the number of surface grid points used. The default value is 0.00001. Smaller values result in denser grids.

`dielectric_in`
: The interior (solute) dielectric constant. The default is 1.0, a value typical of peptide systems.

[3] E. Gallicchio, L. Y. Zhang, and R. M. Levy, *J. Comput. Chem.*, **23**, *517–529* (2002)

`dielectric_out`
: The exterior (solvent) dielectric constant. The default is 80.0, a value typical of water simulations.

`hydrogen_radius`
: The atomic radius of hydrogen, used in generating the surface. The default value is 1.0.

2.3.6 Subtask Mixture

- `mixture [ density` *val* `| keep` *num* `] [ overlap` *val*`]`

This command sets optional parameters for the removal of excess solvent molecules when solvent and solute are mixed. If `mixture` is not present then the default is to remove all solvent molecules that overlap (as defined below) with any solute atom. When the `mixture` command is issued only up to a maximum of N solvent molecules are removed. N is calculated in one of two ways. Either from the effective solute volume (which can be controlled using the `density` parameter) or from the number of solvent molecules not to be removed (the `keep` parameter). A molecule is considered for removal if the ratio of the distance d and the sum $R1 + R2$ of the van der Waals radii of any atom of the solvent molecule and any atom of the solute is smaller than a overlap threshold value (the `overlap` parameter). If the minimum distance d is larger than 10 Å a solvent molecule is not considered for removal regardless of the value of the overlap threshold value. If more than N solvent molecules are flagged for removal only the N solvent molecules with the smallest minimum distance d are removed. If instead the number of solvent molecules flagged for removal is less than N all flagged solvent molecules are removed.

`density`
: Keyword `density` is used to set the solute density. The default is $1\,\mathrm{g/cm^3}$. The volume of solvent removed is equal to the effective volume of the solute. The effective solute volume is calculated from the solute mass and the solute density. The larger the solute density the smaller the effective solute volume and thus the smaller the maximum number N of solvent molecules to be removed.

`keep`
: Keyword `keep` is used to set explicitly the minimum number of solvent molecules remaining after removal. The default is 0. The maximum number N of solvent molecules to be removed is set as the current number of solvent molecules minus the number of solvent molecules to keep. The `keep` option preempts the `density` option if both are given.

`overlap`
: The `overlap` option is used to set the overlap threshold value below which a solvent atom is considered to overlap with a solute

atom. The default is 1. Decreasing the overlap parameter makes it less likely for two atoms to overlap.

2.3.7 Subtask Solute

This subtask is used to place solute molecules at certain positions in the container "box" of solvent used for the simulations.

2.3.7.1 Translate

The keyword `translate` brings the center of mass (COM) of the system of solute molecules to the origin (center of the box), and also finds the longest distance between atoms along the principal axis, which determines the box edge lengths. The option `skip` says to ignore the last *num* residues of the solute when performing the operation. With `rotate`, the solute is rotated so that the principal moments of inertia coincide with the x, y, z axis. The longest axis of the molecule is oriented along the z axis. `Skip` has the above meaning. If `rotate diagonal` is given on the command line the rotation is such that the principal moment of inertia lies along the diagonal of the simulation box (which must be cubic for this option to work).

- `solute translate [ rotate [ diagonal ] ] name` *spec* `[ skip` *num* `]`

Caution: `skip` *num* excludes residues that may not have meaningful coordinates yet (such as counterions) from the translation/rotation operation. This parameter may be read in for as many different species as necessary. The value given for `skip` means that the last *num* residues of the species are ignored in the translation/rotation of the solute.

2.3.7.2 Read

The keyword `read` is used to read in COM coordinates of the solute.

- `solute read xcm` *val* `ycm` *val* `zcm` *val*

2.3.8 Subtask Solvent

Build solvent system.

- `solvent new [ bx` *val* `by` *val* `bz` *val* `] [density` *val*`]`
- `solvent old read` *fname* `[ bx` *val* `by` *val* `bz` *val* `] [ place charge name` *spec* `-`
  `positive` *num*`+ negative` *num*`-  [ electrostatics ] [ cutoff` *val* `] ]`

`new` Create a set of coordinates for solvent atoms provided box edge length (b_x, b_y, b_z) and bulk density (g/cm^3) of solvent. Molecules are placed on a cubic lattice.

`old` Reads in solvent coordinates and box edge length from a pre-existing file *fname*, such as '`spchoh.dat`' or '`tip4p.dat`'. The system is enhanced and/or clipped to the right size specified by the `bx`, `by`, `bz` parameters.

`bx,by,bz` Length of box edge in x, y and z directions.

`place` Charges may be placed at this time using the keyword `place charge`, where the program will read the number of positive and negative charges to be placed. (see Notes below).

`electrostatics`
`Electrostatics` dictates that the added charges will replace those solvent molecules having the highest electrostatic potential due to all solute molecules.

`cutoff` `Cutoff` is used in the placement of ions and affects the calculation of the electrostatic potential (default = 0.0).

Notes:

1. If the system is a mixture, the program uses default values for b_x, b_y, and b_z based on the longest distance along the principal axes calculated for the solute system when the command `solute translate` was executed. (Actually, $b_x = l_x + dx$, $b_y = l_y + dy$, $b_z = l_z + dz$, where l_x, l_y, l_z are longest distance along the principal axis, and dx, dy, dz are margins to allow at least two layers of solvent molecules in between the solute and box wall).
2. If the `solute` subtask precedes this command, the solvent molecules overlapping with solute atoms are removed.
3. The keywords `place charge` assumes that the ions have been built in task `create` (`build primary ions`) with the positive ions built first and then the negative ions.

2.3.9 Subtask Zonecons

This subtask is used to constrain (*freeze*) or restrain (*buffer*) various regions of a molecule based on options specified by the user.

- `zonecons [ auto | [ [freeze|genbuffer] | chain | resseq | -`
  `residue | atom | sphere ] name` *spec sub-options* `]`

There are seven types of `zonecons` subtasks described below. All but `zonecons auto` are additive, so you can use combinations of them. By default, all atoms are free to move, as if there are no `zonecons` subtasks at all.

Any buffered atoms are restrained using an harmonic potential centered on the original atom position. Any atom position can be restrained this way. A buffer zone is often used to to define an intermediate zone between a fixed region where the atom positions are frozen and the free region where the atom positions are not restrained. The buffer option is also often used to perform constrained minimizations. The force constant of the restraining harmonic potential is user selectable, see Section 2.3.4.3 [Weight (setpotential)], page 48.

2.3.9.1 Auto

Use the frozen/buffered settings from an input Maestro file.

- `zonecons auto`

Maestro files written by Maestro specifically for FirstDiscovery jobs, or written as output from a FirstDiscovery job, will contain an extra parameter (internally named `i_i_constraint`) for each atom. `Zonecons auto` uses this parameter in lieu of any other zonecons option, where the values 0, 1, and 2 correspond to free, frozen, and buffered, respectively.

2.3.9.2 Freeze/Genbuffer

Freeze or restrain (buffer) a specified group of atoms, e.g., all heavy atoms, all C atoms, all N atoms, all O atoms, or all atoms.

- `zonecons [freeze|genbuffer] name` *spec* `[all | allC | allN | allO | allheavy]`

This is the general freezing or restraining option, it can be used to freeze/restrain all atoms, all carbon atoms, all nitrogen atoms, all oxygen atoms, or all heavy atoms. The general restraining option is called `genbuffer` to differentiate it from the `buffer` designation available in some of the other `zonecons` options.

2.3.9.3 Chain

Chain-based scheme, select any chain in a protein to be in fixed, free, or buffer region

- `zonecons chain name` *spec* `[chainname` *name* `[fixed|free|buffer] ]+`

This is the chain option, which is used to classify the whole chain with *name* to be in fixed, free, or buffer regions.

2.3.9.4 Resseq

Residue sequence-based scheme, such as from residue number 20 to 50, to be in fixed, free, or buffer region

- `zonecons resseq name` *spec* `[resn` *fres* `to` *lres* `-`
  `[all | allC | allN | allO | allheavy] [fixed|free|buffer] ]+`

This is the residue sequence option, which states that in the specified residue sequence, starting from first residue *fres* to last residue *lres*, the specified atom types (all atoms, all carbons, etc.) are to be in fixed or free or buffer regions.

2.3.9.5 Residue

Residue-based scheme, such as backbone, sidechain, or amide of a residue to be in fixed, free, or buffer region

- `zonecons residue name` *spec* `[resn` *num* `-`
  `[all|backbone|sidechain|amide|Calpha|Ncap|Ccap] [fixed|free|buffer] ]+`

This is the residue option, which states that in the specified individual residue(s), with residue number(s) *num*, the specified atoms (all, backbone, sidechain, amide, α carbon, etc.) are to be in fixed or free or buffer regions.

2.3.9.6 Atom

Atom-based scheme, for any particular atom

- `zonecons atom name` *spec* `[atmn` *num* `[fixed|free|buffer] resadj [0|1] ]+`

The atom option, the lowest level option, which classifies each atom to be in the fixed or free or buffer regions.

The option `resadj` is used for residue-based adjustment; if it equals 1, then the whole residue associated with that particular atom will be classified in the the same region (in this case the residue becomes the basic operational unit). The default value for `resadj` is 0, which means no residue-based adjustment is performed.

2.3.9.7 Sphere

Sphere-based scheme, freeze/relax any atoms inside a sphere with a center and radius

- `zonecons sphere [center x` *val* `y` *val* `z` *val* `| name` *spec* `resn` *num* `atomname` *name*`] -`
  `[freeze | relax ] rad` *rad* `buffrad` *buffrad* `resadj [1|0]`

This is the sphere option, which is used to relax or freeze a sphere with the center located at residue number *num* and atom name *name*, and a radius of *rad*. The *buffrad* is the radius for buffer, the shell between radius *rad* and *buffrad* becomes the buffer region. It should be noted that *buffrad* should be bigger or equal than *rad*.

The option `resadj` has the same meaning as in the atom option, except the default value here is 1, which means the residue-based adjustment is turned on in sphere option by default.

2.3.9.8 Example Zonecons Input

Here is an example for how to use the various options for zone constraints. See Section C.2.1 [Frozen (example)], page 249 for more details.

```
setmodel
   setpotential
     mmechanics
   quit
   read parm file paramstd.dat noprint
   enrg parm cutoff 20.0 -
     listupdate 100 diel 1.0 nodist print 1
   zonecons freeze  name hiv allheavy
   zonecons chain   name hiv chainname A free  chainname B fixed
   zonecons sphere  name hiv resn 20 atomname CA relax rad 10.0 buffrad 12.0
   zonecons residue name hiv resn 10 backbone fixed  resn 11 sidechain free
   zonecons resseq  name hiv resn 20 to 40 all buffer  resn 41 to 100 all fixed
   zonecons atom    name hiv atmn 45 free  atmn 50 fixed  atmn 52 buffer
quit
```

2.3.9.9 Zonecons Keywords

Some of the keywords used above for various `zonecons` subtasks have the following meanings. Not all keywords are appropriate for every `zonecons` option, see the above syntax diagrams for a list of those allowed.

`freeze` General freeze option, to freeze all atoms, all carbons or all heavy atoms.

`chain` Chain option, to freeze/relax/buffer proteins by chain name.

`resseq` Residue sequence option, to freeze/relax/buffer proteins by residue sequence.

`residue` Residue option, to freeze/relax/buffer a residue's backbone, sidechain, etc.

`atom` Atom option, to freeze/relax/buffer any particular atom.

`sphere` Sphere option, to freeze/relax a sphere with a center and a radius.

`free` Free to move.

`buffer` In the buffer region.

`fixed` In the frozen region.

`resadj` Residue based adjust, default value is 0 for atom level option, and 1 for sphere level option. If it equals 1, then the whole residue will share the same region with one or more atoms specified by the `zonecons` subtasks.

`allC` All carbon atoms.

`allN` All nitrogen atoms.

`allO` All oxygen atoms.

`allheavy` All heavy atoms, atoms except H.

`backbone` Backbone atoms in a residue.

`sidechain`
Sidechain atoms in a residue.

`amide` Amide group atoms in a residue.

`Calpha` Alpha carbon atom in a residue.

`Ncap` N-terminal cap in a residue (NH2, NH3+).

`Ccap` C-terminal cap in a residue (COOH, COO-).

`center` To read in the cartesian coordinates of a sphere center directly. The center can also be read in by specifying an atom name `atomname` in a residue `resn` in a specie `name` *spec*.

`rad` *value* Radius of frozen or free zone.

`buffrad` *value*
Radius of buffer zone. The value of *buffrad* should be bigger than *rad*.

`chainname` *name*
Chain name to be relaxed or fixed.

`atomname` *name*
Name of atom at center of sphere.

`resn` *fres* `to` *lres*
Starting from first residue *fres* and ending with last residue *lres*

Please note: `resn` (or `resnumber` or `rnumber`) residue numbers supplied in the main input file have the following meanings: positive numbers mean the residue numbering used in the original PDB file; negative numbers mean the reordered Impact residue numbers, i.e., sequential, starting with 1; 0 means all applicable residues.

Caution: The `zonecons` option alters many structural arrays. It is assumed that all bonds angles and torsions that lie completely in frozen regions will not change and therefore their entries in the structural arrays are deleted. Also, in later energy calculations non-bonded or hydrogen bond pairs for which both atoms are frozen are not stored or calculated.

2.3.10 Subtask QMregion (QSite)

The QSite module allows a section of a protein and/or whole ligand(s) to be treated quantum mechanically while the rest of the system is treated by OPLS-AA. Gas phase 6-31G* Hartree-Fock (HF) and DFT energies, minimizations, and transition state optimizations are currently implemented for

all amino acids, ligands, ions, and bound waters. Single-point LMP2 calculations are also supported. QSite solvation using continuum solvent (PBF model) are possible as well.

2.3.10.1 QSite Overview

The QM/MM interface consists of a frozen localized single-bond QM molecular orbital at each QM/MM boundary.[4] The QM and MM regions interact via a Coulomb interaction (between MM charges and the QM wave function) and a van der Waals interaction (van der Waals parameters are employed for both the QM and MM atoms). In addition there are QM/MM hydrogen bonding terms. Specialized MM-like correction parameters are used for stretches, bends, and torsions involving atoms that touch or span the QM/MM interface. These parameters are fit to reproduce local-MP2/cc-pVTZ(-f) quantum chemical conformational energetics of each residue.

A QSite job requires both Impact and Jaguar input files. The job is initially launched using the Jaguar program driver script `jaguar`. Once Jaguar detects that it is doing a QSite job, it calls Impact, which then reads the main input file (with protein, ligand data) and the QM region specifications. Impact calculates the requisite MM energy/gradient terms and creates a Jaguar input file for the QM region only. Control is then passed back to Jaguar, which calculates the total QM portion of the QM/MM energy/gradient.

QSite geometry optimization uses an adiabatic approach. This means that a full minimization of the MM region is performed by Impact before each QM geometry step taken by Jaguar. During the QM step all of the MM region except for a few atoms at the QM/MM interface are frozen in the QM optimization/geometry steps and similarly the QM region is frozen in the MM optimization process.

The following subsections describe the Impact and Jaguar QM/MM inputs and illustrate the execution of a QSite run.

Here is the general syntax for the `qmregion` subtask:

- `qmregion [ residue name` *spec* `mole` *mol* `[ all | resn` *num* `chain` *chainid* `insert` *insertion_code* `molid` *num* `[ cutb` *num* `] ]`
- `qmregion atom name` *spec* `mole` *mol* `atom` *num*
- `qmregion ion name` *spec* `ionn` *num*

2.3.10.2 QM protein region

The QM region of the protein is specified by making QM/MM *cuts* or boundaries at the bonds emanating from the Cα carbon of any residue. In addition,

[4] D.M. Philipp and R.A. Friesner,*J. Comput. Chem.* **20**, *1468* (1999); R.B. Murphy, D.M. Philipp, R.A. Friesner, *Chem. Phys. Lett.* **321**, *113* (2000); and R.B. Murphy, D.M. Philipp, R.A. Friesner, *J. Comput. Chem.* **21**, *1442* (2000).

whole residues can be designated as QM as long as they are inside the bondaries of QM/MM cuts at more distant residues. The 6 types of cuts and associated QM/MM regions are defined as follows and as depicted in the following figures.

Cut 1: The Cα-N bond forms the boundary, and the Cα atom and its attachments are in the QM region.

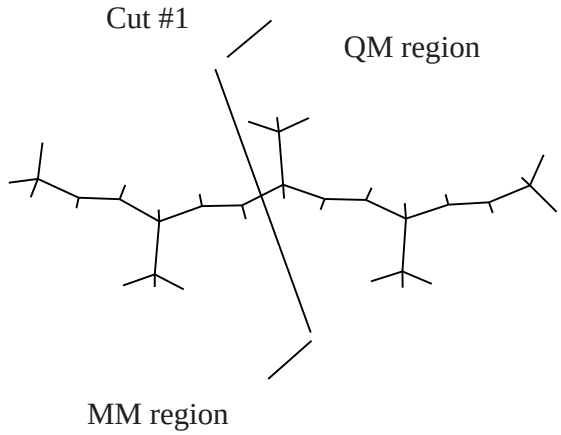


Figure QMMM−1; QM/MM regions
for backbone cut type 1.

Cut 2: The Cα-C bond forms the boundary, and the Cα atom and its attachments are in the QM region.

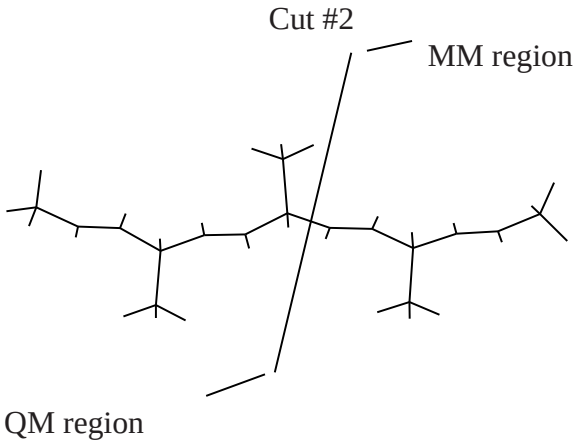


Figure QMMM−2; QM/MM regions
for backbone cut type 2.

Cut 3: The Cβ-Cα bond forms the boundary, and the side chain is the QM region.

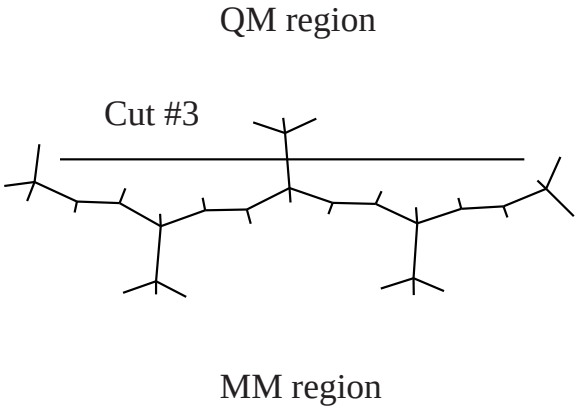


Figure QMMM−3; QM/MM regions for side chain cut type 3.

Cut 4: The N-Cα bond forms the boundary, and the amide nitrogen (N) and its attachments are in the QM region.

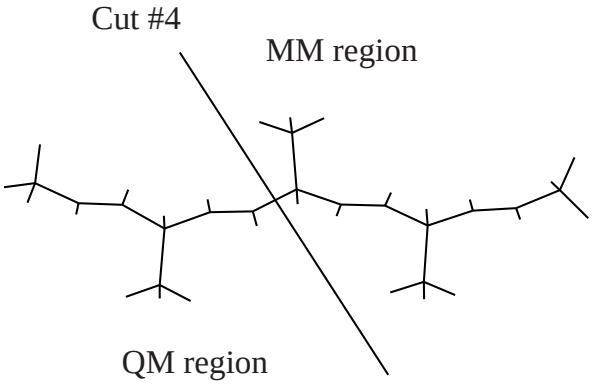


Figure QMMM−4; QM/MM regions for backbone cut type 4.

Cut 5: The C-Cα bond forms the boundary, and the carbonyl carbon (C) and its attachments are in the QM region.

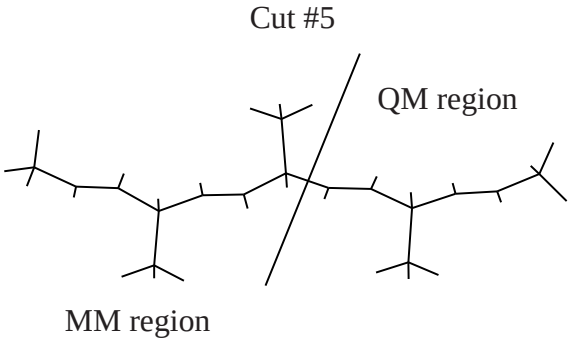


Figure QMMM−5; QM/MM regions
for backbone cut type 5.

Cut 6: The whole residue is QM, and QM/MM cuts are made on the preceding (type 5) and following (type 4) residues. Alternatively, the two separate cuts can be specified for their residues.

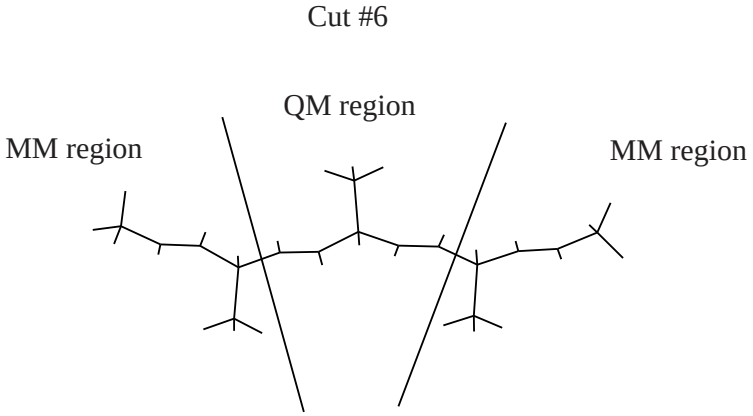


Figure QMMM−6; QM/MM regions
for backbone cut type 6.

Except for side chain cuts (type 3), the cut residue must be connected to another pure (no cut) QM residue. Placing backbone cuts in consecutive

residues is not recommended since the bondary regions will interact too strongly.

Sidechain cuts in the following residues are *not* allowed: ARG SER PRO GLY and ALA. To treat these sidechains as QM regions, place backbone cuts on the residues adjacent to the desired one in this set.

As an example, suppose the ala-gly-ser section of a . . . lys-ala-gly-ser-phe. . . protein is to be represented in a QM fashion. In this case a cut of type 5 (or 1 to include the lys sidechain in the QM region) would be made in lys, and a cut of type 4 or (2 to include the phe sidechainin the QM region) in phe. In addition, residues ala-gly-ser would all be specified as QM. More commonly a set of sidechain cuts of type 3 might be made for residues that make important contacts with a ligand to allow the contact regions and the ligand all to be treated quantum mechanically.

If a side chain cut (type 3) is requested for ser, ala, thr, or gly residues, backbone cuts of type 6 instead will automatically be made in the adjacent residues and the whole ser, ala, thr, or gly residue is included in the QM region. This scheme has been implemented because it is difficult to properly parameterize a very short QM sidechain region.

The protein QM regions are specified in task `setmodel` with the syntax;

```
qmregion residue name prot mole pro resn 142 cutb 3
```

This directive places the sidechain of residue 142 in species *prot*, molecule *pro* in the QM region. The integer following `cutb` specifies the type of cut to be made.

Alternatively, the whole residue can be made QM (no cut) by omitting the `cutb`-*value* pair:

```
qmregion residue name prot mole pro resn 142
```

The QM/MM interface requires that each protein segment of the QM region be defined either by a single cut of types 3 or 6, or by matching cut specifications for the N- and C-terminal residues of the segment in question. In the latter case, all intervening residues must explicitly be specified as QM in `qmregion` specifications.

Note that QSite requires that the whole system fit into one Impact species. This can be done by putting molecules (proteins or ligands) into one species using the `mole` notation. QSite calculations can be carried out with PBF (but not SGB) implicit water or can be run with the *bound* waters typically found in PDB files. Solvent boxes, which require periodic boundary conditions, however, cannot be used.

2.3.10.3 QM whole ligands

A ligand can be designated as a pure QM region with the syntax;

```
qmregion residue name prot mole lig all
```

where molecule *lig* is a ligand in species *prot*. The `all` syntax designates the whole ligand as a QM region. Note that QM/MM boundaries cannot currently be made between ligand atoms.

2.3.10.4 QM bound waters

Making one or more bound waters QM can be accomplished by building the desired water(s) as molecule(s) of type ligand by using an associated water PDB file inside the CREATE section. For example,

```
CREATE
..
build primary name prot type ligand mole water read file water.pdb
..
```

builds a water molecule (or molecules) as a ligand with coordinates as given in '`water.pdb`'. The QM specification in task `SETMODEL` is:

```
qmregion residue name prot mole water all
```

2.3.10.5 QM Ions

Ions can be included in the QM region first by building the ion or ions. The following illustrates the placement of a Zn2+ ion:

```
CREATE
...
build newres zn2+ file zn
build primary ions name prot zn 1 xyz x 36.921 y 44.908 z -7.111 end
...
```

where `build newres` creates a Zn2+ residue with the name `zn` (the 1 following `zn` is a specification for one ion), and `build primary ions` adds the ion into the previously defined molecule of the species *prot* at coordinates (x,y,z). The specification of the ion as a QM region is done as follows;

```
qmregion ion name prot ionn 1
```

specifies that ion number (`ionn`) "1" of species *prot* should be treated as a QM ion. When multiple ions are present, one such `qmregion` directive should be given for each ion that is to be QM.

The following example from a calculation on thermolysin with a QM ligand, Zn ion, bound waters, and several QM side chains illustrates all of the QM specifications;

```
CREATE
  build newres zn file zn
  build primary name prot type protein mole pro read file 8tln.nolig.pdb
  build primary ions name prot zn 1 xyz x 36.921 y 44.908 z -7.111 end
  build primary name prot type ligand mole water read file water.pdb
  build primary name prot type ligand mole lig read file lysval.pdb
  read coordinates name prot mole pro brookhaven file 8tln.nolig.pdb
  read coordinates name prot mole water brookhaven file water.pdb
  read coordinates name prot mole lig brookhaven file lysval.pdb
QUIT

SETMODEL
  setpotential
    mmechanics
  quit
  read parm file paramstd.dat noprint
  energy parm cutoff 100.0 listupdate 100 diel 1.0 nodist
  qmregion residue name prot mole water all
  qmregion residue name prot mole lig all
  qmregion ion name prot ionn 1
  qmregion residue name prot mole pro resn 142 cutb 3
  qmregion residue name prot mole pro resn 146 cutb 3
  qmregion residue name prot mole pro resn 166 cutb 3
QUIT
```

2.3.10.6 Basis set specifications.

All of the standard basis sets used in Jaguar are available for the QM region of a QSite setup. Then basis sets can be specified within the Impact input as follows.

The default basis used is 6-31G* (LACVP* for metals), which **must** be entered into the Jaguar input file (see below) regardless of other basis set specifications. To specify the basis on a particular residue the following syntax applies:

```
SETMODEL
  ..
  qmregion residue name dipep resn 2 cutb 3
  ..
  basis name dipep resnumber 2 basis cc-pvtz(-f)
  ..
QUIT
```

This will setup a cc-pvtz(-f) basis on the QM atoms of previously specified QM residue 2. Note that atoms comprising the QM/MM cut and their

bonded neighbors will automatically stay at 6-31G*. This restriction is necessary since the QM/MM boundary region is parametrized with 6-31G*. The code will automatically keep the necessary 6-31G* basis sets regardless of basis set specifications made by the user.

The syntax for changing the basis set within a specified radius of a chosen atom is:[5]

```
SETMODEL
  ..
  qmregion residue name dipep resn 2 cutb 3
  ..
  basis name dipep resnumber 2 atname CE1 radius 5.0 basis cc-pvtz(-f)
  ..
QUIT
```

will change the basis set to cc-pvtz(-f) on atoms with 5 Å of atom CE1 in previously specified QM residue number 2.

2.3.10.7 QSite energy/minimization:

Single point QSite energies can be obtained using task `analysis` with the subtask `qmme`, e.g.,

```
ANALYSIS
  qmme
QUIT
```

will tell Impact to generate a QM/MM energy.

QSite geometry optimizations require the usual Impact MM minimization section, e.g.:

```
MINM
  conjugate dx0 0.05 dxm 3.0 rest 50
  input cntl mxcyc 10000 rmscut 1.9e-1 deltae 0.5
  run
QUIT
```

with no special QSite flags.

2.3.10.8 QSite Transition State Optimization

QSite can perform optimizations to transition state structures using three different methods. The method you choose will depend on what starting structures you have. See the *Jaguar User Manual* for more information on these methods.

[5] N.B.: The radius option is not available via Maestro, but you can add it by hand into the input file

Standard method

If you only have an initial guess structure for the transition state, QSite can find the saddle-point closest to the starting structure by maximizing the energy along the lowest-frequency mode of the Hessian and minimizing the energy along all other modes.

Linear Synchronous Transit (LST) method

If you have structures for the reactant and product, then QSite can use a quasi-Newton method to search for the optimal transtion state geometry. Given the two endpoint structures, and an interpolation value between 0.0 ($\equiv$ reactant structure) and 1.0 ($\equiv$ product structure), QSite will try to construct an initial transition state structure at that point along the reaction coordinate.

Quadratic Synchronous Transit (QST) method

If you have structures for the reactant, product, and transition state guess, then QSite will use the same quasi-Newton method as LST does, but will use your initial guess for the transition state, rather than interpolating as in LST.

Impact input file keywords:

- `qmtransition [ reactant | product ] file` *fname* `[ gotostruct` *number* `]`

These keywords are necessary in the Impact input file when you have multiple structures to include in your calculation, as is required in both LST and QST. LST calculations require the reactant to be loaded in a normal `build primary` command, and the product structure to be defined with a `qmtransition` keyword thus. QST calculations require the transition state guess structure to be loaded by `build primary`, and both the reactant and product structures defined by `qmtransition`.

Jaguar input file keywords:

```
&gen
igeopt = 2
iqst = [ 0 | 1 | 2 ]
qstinit = interpolation_value
&
```

These keywords are actually Jaguar keywords; see the Jaguar documentation for more information. Briefly, `igeopt=2` tells Jaguar to do a transition state optimization rather than a minimization. `iqst` indicates which optimization method is to be used, standard, LST, or QST, respectively. The LST method calculates an initial guess structure by interpolating between the reactant and the product, the `qstinit` parameter indicates where along the reaction coordinate this structure should lay; the default is 0.5 (midway between).

2.3.10.9 Jaguar input section:

CAUTION: do not use the "qmme" energy option with a MINM section, they are not compatible and their simultaneous use will cause erroneous gradients.

QSite calculations also require a short Jaguar input file specifying options specific to the quantum region such as the charge and multiplicity of the quantum region.

The prototypical input file for running a gas phase QSite optimization looks like:

```
&gen
mmqm=1
idft=22111
basis=6-31G*
molchg=2
igeopt=1
&
```

where `mmqm=1` signifies to Jaguar that a QSite calculation is requested, `idft=22111` requests thar the B3LYP functional be used. Other DFT methods should not be used with QSite. The `basis=6-31G*` basis specification is mandatory and will be properly overriden by any basis set specifications made in the Impact input file as discussed above. `molchg=2` is the charge of the QM region (the Jaguar `multip=` keyword would be included if the QM region had a net spin), `igeopt=1` is the keyword to request a QSite geometry optimization (note that the Impact input file also requires a minimization section).

The QSite Jaguar input file for a solvation run consists of

```
&gen
mmqm=1
basis=6-31G*
igeopt=1
isolv=2
nogas=2
&
```

where `isolv=2` requests a PBF solvation calculation and `nogas=2` omits a preliminary gas phase optimization normally done in pure QM solvation geometry optimization calculations. The `nogas=2` option will be set automatically in Jaguar 4.1[6]. The `consolv pbf` keyword must also be present in the Impact input file as it is for pure MM solvation calculations.

[6] Jaguar v4.0 releases later than r21 will also set this automatically.

2.3.10.10 Running QSite

QSite jobs can be run from the command-line by giving both input files to the `impact` script. The syntax for running a QSite job is then:

```
% impact -j job.jaguar.in -i job.impact.inp -o job.log
```

where *job.jaguar.in* is the Jaguar input file name (e.g. '`peptide.in`') and *job.impact.inp* is the Impact input file name.

The QM/MM output contains the QM and most of the MM output will appear in '`job.jaguar.out`' and the intermediate Jaguar output will appear in '`job.jaguar.log`' as the job runs in the scratch directory (the Jaguar scratch directory is set in the '`$SCHRODINGER/jaguar.hosts`' file. The QM/MM energy in the Jaguar output file has the heading;

```
Total QM-MM Energy:  -3390.09684895821 hartrees
```

Solvation energies also appear in the Jaguar output file as:

```
sfinal:  -2415.0483 kcal/mol
```

where `sfinal` is the solvation energy of the QM/MM system in water relative to the gas phase.

In addition the total QM/MM solution phase energy is specified in the Jaguar output as:

```
(P)  Solution phase energy........  -428.00832706556  (Q+R+S).
```

The solvation energies printed in the Impact output of a QM/MM run are not the QM/MM solvation energies.

The detailed requirements for running QSite are as follows. The QSite job is lauched as a Jaguar job using the `jaguar` run script which should be in the `$SCHRODINGER` directory. The Impact and Jaguar inputs should be in the same directory by default. If it is desired to keep the Impact information in a separate directory, the following lines should be added to the Jaguar input file

```
&impact
mmdir=/wherever/you/want/the/data
&
```

In general however, you will want to keep all your Schrödinger software grouped together.

3 Perform Simulations

This chapter describes tasks that perform real Impact simulations: energy minimization, molecular dynamics, Monte Carlo etc. Various new technologies were implemented in these tasks, such as Fast Multipole Method (FMM), Multiple Time-step Algorithm r-RESPA, Poisson-Boltzmann Solver PBF, Surface Generalized Born Model SGB, J-Walking/S-Walking Method, etc.

3.1 Task Minimize

Minimize a system using either the steepest descent or the conjugate gradient method. This task may only be called after the structural arrays have been filled and after a potential energy function has been set using `setpotential`. This task is used in many of the included examples.

Results are printed every 10 steps by default, but this value can be adjusted via the `enrg` `parm` `print` keywords in the `SETMODEL` task (see Section 2.3.1.5 [Parm], page 40).

Example:

```
minimize
   read coordinates formatted file fname
   steepest dx0 value dxm value deltae value
   run
   plot indiv quit
   write coordinates formatted file fname
quit
```

3.1.1 Subtask Steepest

Use the steepest descent algorithm for energy minimization of a system.

- `steepest dx0` *value* `dxm` *value*

`dx0` Initial step size (default = 0.05).
`dxm` Maximum step size (default = 1.0).

3.1.2 Subtask Conjugate

Use the conjugate gradient algorithm for energy minimization.

- `conjugate dx0` *value* `dxm` *value* `maxit` *number*

`dx0` *step_size*
Set the initial step size (default = 0.05).

`dxm` *step_size*
: Set the maximum step size (default = 1.0).

`maxit` *step_size*
: Maximum number of iterations for line search (default = 3).

`rest`
: Frequency of restarting with steepest descent (default = number of atoms ×3).

3.1.3 Subtask Tnewton

Use the truncated Newton algorithm (copyright (c) 1990 by Tamar Schlick and Aaron Fogelson, updated November 1998 by Dexuan Xie and Tamar Schlick, used by permission)[1] for energy minimization.

PLEASE NOTE: This minimization algorithm cannot currently be used with the Fast Multipole Method (FMM) (see Section 2.3.4.1 [Mmechanics], page 41) or molecular cutoffs (see Section 2.3.1.2 [Molcutoff], page 38).

- `tnewton [nfull` *number*`] [nhscale` *number*`] -`
  `[verbose` *number*`] [tncut` *value*`]`

`nfull`
: Number of minimization steps per update of the long-range forces (as defined by the `tncut` value). The default is 10, and values higher than 20 are not recommended. Setting `nfull` too high can result in unrealistic structures and/or failure of the minimization. The short-range forces are updated at every minimization step.

`nhscale`
: Scale factor for the size of the Hessian matrix. The amount of memory allocated for this matrix will be the `nhscale` value times the number of atoms in the system. The default is 50.

`verbose`
: Controls the amount of printing. The default is 0. A positive value will result in a large amount of output, and is not recommended in general.

`tncut`
: Cutoff distance between short-range and long-range forces. Forces between atoms more distant than this will be calculated only every `nfull` minimization steps, as opposed to every step for the short-range forces. The default is 10.0 Å.

3.1.4 Subtask Input

This subtask inputs parameters necessary for the minimizer.

[1] For details, see Xie, D. and Schlick, T., "Remark on the Updated Truncated Newton Minimization Package, Algorithm 702," ACM Trans. Math Softw., 25, 108-122, March 1999, and Xie, D. and Schlick, T., "Efficient implementation of the truncated-Newton algorithm for large-scale chemistry applications," SIAM J. Opt., 10: 132-154, October 1999.

- `input cntl [ mxcyc` *num* `] [ rmscut` *val* `] [ deltae` *val* `]`

`mxcyc` The maximum number of cycles for the minimization (default = 100).

`rmscut` Criteria for convergence of the RMS gradient (default = 0.01).

`deltae` Criteria for convergence of the change in energy for each atom, average over the whole system (default = $1.0 \cdot 10^{-7}$).

Important Notes:

1. The values for both `rmscut` and `deltae` must be met before a run is converged.
2. The minimization will stop when the convergence criteria are met.

3.1.5 Subtask Run

This command signals the program to start running the minimization. All other parameters must be set correctly before `run` is executed.

3.1.6 Subtask Plot

Use the standard plot routines to plot energies of a system in a graphical output format. This command must be performed after the `run` command is invoked.

- `plot [ individual | superimpose | group ] postscript file` *fname*
- `plot [ individual | superimpose | group ] lineprint [ file` *fname* `]`

`individual`
Plots each individual energy term vs. cycle number.

`superimpose`
Superimposes all energy terms on one plot.

`group` Superimposes groups of terms as follows:

1. Bonds, angles, torsions, and 1-4 terms.
2. Constraints.
3. Nonbonded—Lennard-Jones, electrostatics and Hydrogen-bond.

Caution: The `plot` options described above are specific to the `minimize` task. The `delay`, `postscript` and other `plot` options are described in detail in Section B.1 [Plot (plot)], page 231.

3.1.7 Subtasks Read and Write

Impact provides the `write` command to save to a file the molecular system coordinates in several formats. The `write` and `read` commands also offer a simple way of saving a snapshot of the system (coordinates and, if so desired, velocities) and restoring it afterwards.

The following description applies not only to task `minimize` but also to `dynamics`, and `montecarlo`, although in some cases (to be discussed below) not all options would make sense. There are three types of file that can be used to hold snapshots of the system: PDB (`brookhaven` or `impact` format), Maestro, *residue template*, *restart* and *trajectory* files.

To write a PDB file use the following syntax:

- `write pdb [ brookhaven | impact | nil ] -`
  `name` *species_name* `file` *filename*

Note: only coordinates can be written to a PDB file. To read a PDB file you must do so inside the `create` task.

To write a Maestro file use the following syntax:

- `write maestro [ name` *spec1* `[ name` *spec2*`] ] -`
  `file` *filename*

If the species to be written to the Maestro file are of type '`auto`' the information from the original Maestro file (or as converted from a PDB or SD file) is preserved in the output of this command. If the species is of type other than '`auto`', Impact attempts to generate a valid Maestro file by creating a type '`auto`' temporary copy of the species before writing it to the file. If two species are specified, a temporary species of type '`auto`' obtained by merging the two species is written to the file. In absence of species specification the default is to merge both Impact species in the output file. To read a Maestro file you must do so inside the `create` task.

To write a residue template file (see Section A.2 [Residue files], page 221) use the following syntax:

- `write template name` *spec* `file` *filename*

where *spec* is the name of the species to be written and *filename* the name of the file to be created. This command is most often used to generate a residue template file to be used as input for the `build newresidue` (see Section 2.2.1.8 [Newresidue (build)], page 27) command of the `CREATE` task. Despite the name, residue template files can hold the structure of any molecule not just those of aminoacid residues. Residue template files are in free format and can be edited to, for instance, manually change the assigned atom types and partial charges. **Caution:** `write template` only works with the *non-default* OPLS1999 and OPLS2000 force fields.

The `write restart` and `read restart` commands are used to save and restore the coordinates (and velocities) of all particles in the system. A restart file consists of a snapshot of the cartesian coordinates and, optionally, ve-

locities of each atom of the system. When reading or writing restart files the behavior of Impact depends on the current task unless the files are written and read using the `external` keyword, in which case Impact honors all requests made on the command line.

- In task `minimize` only coordinates can be written or read. If the command line also specifies velocities Impact will not honor the request unless `external` format is used, although no error will be generated.
- In task `montecarlo` only coordinates can be written but both coordinates and velocities can be read.[2]
- In task `dynamics` velocities are always written to a restart file, even if they are not specified on the command line. The user can, however, choose not to read them back.

In all cases the usage is the same:

- `[ read | write ] restart coordinates [ and velocities ]`
  `[ box | nobox | nil ] -`
  `[ formatted | unformatted | external | nil ] -`
  `[ real8 | real4 | inte2 | nil ] -`
  `file` *filename*

The meaning of the keywords is explained below.

A trajectory file contains a sequence of snapshots of the system (coordinates and, sometimes, velocities of all atoms). Normally trajectory files are read using the `table` subtasks `starttrack` and `stoptrack` but they can also be read wherever a restart file can be read.

- `write trajectory coordinates [ and velocities ] [ box | nobox | nil ] -`
  `[ unformatted | external | nil ] -`
  `[ real8 | real4 | inte2 | nil ] -`
  `file` *filename* `-`
  `every` *number_of_steps*
- `read restart coordinates [ and velocities ] [ box | nobox | nil ] -`
  `[ unformatted | external | nil ] -`
  `[ real8 | real4 | inte2 | nil ] -`
  `file` *filename* `-`
  `skip to` *frame_number*

Caution: reading a frame (snapshot) from a trajectory file using the last syntax shown should be done with care, since strange things may happen if the user mixes the coordinates with the velocities.

`formatted`
`unformatted`
`external` (default for restart and trajectory files) A `formatted` file is an `ASCII` file containing the list of coordinates (and velocities, if appropriate). The main advantage of these files is that they

[2] Though velocities are not very meaningful in this case.

are human readable, but they usually occupy too much space. An `unformatted` file, on the other hand, is binary and thus much smaller. The main disadvantage is that files generated on one machine are usually not readily read on other machines. This prompted the development of the `external` way of writing restart and trajectory files, which offers a compact (since it is binary), machine-independent representation. This is the default for trajectory files and it is strongly recommended (`unformatted` files may not be supported in the future). As mentioned above, if the keyword `external` is specified Impact honors all requests on the command line.

`inte2`
`real4`

`real8` (default)
: These keywords control the size of the data written to (read from) a binary restart or trajectory file. When reading an `unformatted` file they must be specified, but that is not necessary when reading an `external` file since the program can find this information from the file itself. The keyword `inte2` will be ignored when reading or writing an `external` file and `real4` will be substituted instead. The sizes are chosen as follows:

  `real8` — Store the data as `real*8` numbers. This is the highest precision available and uses the most disk space.

  `real4` — Stores the data as `real*4` numbers. This halves the storage requirements and also reduces the precision.

  `inte2` — This option is somewhat more complicated. The numbers will be scaled by 1000. and stored as `integer*2` numbers. This will leave a maximum of 5 significant figures and maximum values of ± 32.767.

`[ box | nobox | nil ]`
: Write (or don't write) the dimensions of the simulation volume with the coordinates (these dimensions are needed when performing constant pressure simulations). If a constant pressure simulation is being run, `box` is the default; otherwise it is `nobox`. This option applies to `trajectory` and `restart` files.

`every` *number_of_steps*
: Determines how often coordinate sets will be written.

`skip to` *frame_number*
: When reading a trajectory as a restart file one can specify which frame (snapshot) to read. Frame numbers start at 1 and should not exceed the number of frames that were written to the file.

3.2 Task Dynamics

The object of task `dynamics` is to perform a molecular dynamics (MD) simulation for a system prepared by tasks `create` and `setmodel`. Complete examples of this task are shown in Section C.2.5 [Protein-water MD (example)], page 260 and Section C.2.3 [Protein size (example)], page 253. A typical shorter example is the following:

```
dynamics
  input cntl -
    nstep 2000 delt 0.001 relax 0.01 seed 110 -
    stop rotations constant temperature byspecies -
    nprnt 10 tol 2.0e-7
  input target name protein temperature 298.0
  input target name solvent1 temperature 298.0
  read restart coordinates and velocities formatted file oldrun.xv
  run
  write trajectory coordinates and velocities every 10 -
    external file newrun.xv
quit
```

Please Note: Dynamics simulations may not give useful results, or may terminate with errors, if the initial structure has steric clashes or other problems. Even structures that have been minimized with other programs, or those produced by Maestro's build panel, may have such problems as measured with Impact's force fields. A short Impact minimization task prior to dynamics is useful for fixing such problems.

3.2.1 Subtask Input

Reads in program control parameters for the MD run.

- `input cntl nstep` *steps* `[ delt` *time_step* `]`
- `input cntl [ constant -`
  `[ temperature [ byspecies ] [ relax` *value* `] | totalenergy ] -`
  `[ pressure [ dvdp` *value* `] [ density` *value* `] | volume ]`
- `input cntl [ initialize temperature -`
  `[ forspecies ( name` *spec* `at` *T_i* `)` for all species `| -`
  `at` *T_i* `] [ seed` *num* `] ] -`
  `[ stop rotations ] [ nprnt` *freq*`) ] -`
  `[ tol` *tolerance* `] [metric` *value*`]`
- `input cntl [ statistics [ on | off ] ]`

  Unless otherwise specified the default is to run MD simulations at constant temperature and volume. This results in coupling the system to an external heat bath (with a temperature that is independent of the species). Using the keyword `byspecies` results in velocity scalings that

are independent for each species. In this case the user should specify an initial temperature for each species using the `forspecies` keyword, and all species should appear on the same (logical) line. Otherwise some of the species will end up with the default initial temperature. If '`constant totalenergy`' is specified instead there will be no scaling.[1]

Specifying '`constant pressure`', as opposed to '`constant volume`', results in coupling to a pressure bath using the algorithm of Berendsen et al. (*J. Chem. Phys.*, **81**, *3684* (1984)). Molecular center of mass coordinate rescaling is implemented. The distances between molecules change proportionally to the change in box size and intramolecular distances remain unchanged. Note that a "molecule" is defined as the entity created by a '`build primary`' command. Center of mass coordinate rescaling is ineffective for systems composed of a single molecule (systems built with only one '`build primary`' command). A solvent species is composed of as many molecules as created by the '`build solvent`' command.

Independent of whether the simulation is run at '`constant temperature`' or '`constant totalenergy`' the user can initialize the temperature of all species (either the same for all or on a per-species basis) with the keywords '`initialize temperature`'. **Caution:** by default the temperature is not initialized since this could result in overwriting the velocities read from a restart file. Right after a `minimization`, the user *should* initialize the temperatures of all species to sensible values. The user *should not* use '`initialize temperature`' though, if there is an external restart file (with both coordinates and velocities) read in.

Several parameters can be specified in the '`input cntl`' line:

`nstep` Number of MD steps (*must* be larger than one!).

`nprnt` Gives the number of steps after which contributions to the energy will be printed out (5).

`delt` Gives the time step in picoseconds (0.001).

`relax` Relaxation time in ps for velocity scaling (if using '`constant temperature`') (0.01).

`seed` Seed to be used to start the random number generator when initializing the temperature of (any) species.

`taup` Relaxation time in ps for volume scaling (if using '`constant pressure`') (0.01).

[1] The total energy may actually not be conserved, due to the effects of a sharp cutoff. In most cases this will lead to an unstable simulation.

`dvdp` Isothermal compressibility $1/V(dV/dP)$, in units of atm^{-1}. The default is the value for water: $4.96 \cdot 10^{-5}$ atm^{-1}. This quantity is needed for constant pressure simulations.

`density` Effective density (g/cm^3) of solute molecules. Needed to compute long-range corrections to the pressure (1.0).

`tol` Tolerance to be used when applying the constraints in `SHAKE` and `RATTLE` ($1.0 \cdot 10^{-7}$).

`stop rotations`
Flag for stopping the center of mass motion. Default is not to stop the center of mass motion.

`statistics on`
`statistics off`
Toggles collection of statistics on the fluctuations of the different energy terms during the simulation. In earlier versions this was always on; now it is off by default.

- `input target temperature` *T_f*
- `input target ( [ name` *spec* `] temperature` *T_f* `)` repeated for all species

Allows the specification of the final temperature (*T_f*) for the whole system or by species. The first form should be used only if the scaling is done on a species-independent basis. If the `byspecies` keyword was used, however, the second form must be used and all the species should appear on the same (logical) line. Multiple '`input target`' lines would result in conflicts.

The actual temperature will fluctuate about the desired value. At each MD step the kinetic energies will be scaled so the temperature will approach the desired value on a timescale determined by the `relax` parameter.

- `input target pressure` *P_f*

Reads in the final pressure (*P_f*) of the system. The same comment as in the previous paragraph applies, *mutatis mutandis*.

3.2.2 Subtask Run

Performs the actual molecular dynamics run. The temperatures are initialized at this step, not when the values are read from the '`input cntl`' line. The user can choose among three different algorithms for the integration of the equations of motion: the Verlet algorithm, which is the default; and two based on the reversible RESPA (r-RESPA) of Tuckerman, Berne and Martyna, *J. Chem. Phys.*, **97** (1992). Currently at most three inner stages are allowed and the frequency with which the corresponding forces are updated is controlled by the parameters *freqf* (fast forces), *freqm* (medium and slow

forces) and *freqs* (slow forces). Currently *freqm* and *freqs* only have meaning if the FMM (fast multipole) code is used. On the other hand, *freqf* can be used with or without the FMM since it controls only the bonding forces. If the FMM is used and *freqs* is present, the forces are separated in three pieces: those arising from nearby bodies; those arising from bodies in the first and second neighbors that are not very close, and those coming from the local expansions. If *freqs* is not present but *freqm* is, the second and third are collected together.

- `run [ verlet | rrespa fast` *freqf* `[ medium` *freqm* `[ slow` *freqs* `] ] ]`

3.2.3 Subtask Plot

- `plot [ individual | group | superimpose ] [ delay | postscript ] -`
  `file` *filename*

  This command is used to `plot` the energy terms generated during a `dynamics` or `montecarlo` run. It must occur after subtask `run`.

  `individual`
  : Plot all individual terms.

  `group`
  : Plot groups of energy terms.

  `superimpose`
  : Superimpose all energy terms onto one plot.

3.2.4 Subtasks Read and Write

Read or Write a) a `restart` file containing final coordinates, and velocities (forces could also be written) or b) a `trajectory` file (see Section 3.1.7 [Read/write (minimize)], page 74).

3.2.5 Subtask Convert

This subtask is provided to ease the transition to the new, default, `external` binary format (see Section 3.1.7 [Read/write (minimize)], page 74).

- `convert -`
  `from [ unformatted | external ] file` *filename* `-`
  `to [ unformatted | external ] file` *filename* `-`
  `[ real4 | real8 | inte2 ] [ box | nobox ] -`
  `[ first` *start* `last` *end* `]`

  Reads a trajectory file written in one format and writes it out in another. The keywords `box`, `nobox`, `real8`, `real4` and `inte2` apply only to the output file and allow the user to specify the corresponding options differently from the ones used when the input file was written (see

Section 3.1.7 [Read/write (minimize)], page 74). Note that `inte2` is the same as `real4` when using the `external` format.

The parameters `start` and `end` allow the user to convert only a portion of the trajectory file. Since both input and output formats can be the same this is a handy way of extracting a consecutive sequence of frames.

3.3 Task Montecarlo

This task performs Monte Carlo simulations on all or parts of a molecule. This task uses Monte Carlo methods to sample conformational space based on the potential function chosen in `setpotential`. An example of the use of this task is Section C.1.5 [MC Refinement (tutor)], page 242.

3.3.1 Subtask Sample

Select torsions to be included in the Monte Carlo sampling. Without this subtask no angles will be sampled! This command must come before `calc`. Use as in the following, noting that in this one task the keywords `fres` and `lres` are **required**, and `fresidue` or `lresidue` are not acceptable;

- `sample alltorsions nseg` *num-nseg* `( fres` *num* `lres` *num* `)` *num-nseg* times `[ minprint ]`
- `sample schain nseg` *num-nseg* `( fres` *num* `lres` *num* `)` *num-nseg* times `[ minprint ]`
- `sample bbone nseg` *nseg* `( type` *angletype* `fres` *num* `lres` *num* `)` *nseg* times `[ minprint ]`

`alltorsions`
: Sample all torsions or side chains, or backbone torsions.

`schain`
: Side chain torsions to be sampled in `proteins`—all χ in residues selected will be sampled except those involving rings (such as `PHE` to `TYR`).

`bbone`
: Backbone torsions to be sampled (Prolines will *never* be sampled).

`nseg`
: Number of residue ranges to be read in.

`type`
: For a protein this keyword can be followed by `phi`, `psi`, `fsi` and `omeg` to respectively sample ϕ, ψ, or ϕ and ψ together, or ω only. The keyword `all` selects all the angles. For DNA `type` can be followed by `all` or `bone` to sample all torsions or just those that do not involve the sugar ring, respectively.

`minprint`
: Turn off the printing of the actual angles sampled. This should only be used on well tested runs where `montecarlo` is used frequently and with the same torsional sampling.

3.3.2 Subtask Params

This command is used to set or change parameters in the Montecarlo run and must be called before the `run` subtask. If `run` is a `restart` and parameters are to be changed, `params` must be after `restart`. **Caution:** changing

parameters in a restart should be done with care, as this can sometimes give strange results! To change more than one of these parameters, use a separate `params` command for each one.

- `params [ step | size | freq | seed | temp ]` *value*

`freq` Frequency of steps to print out data.

`seed` Seed for random number generator.

`step` Number of steps in Monte Carlo run.

`size` Initial angle change; this value will be adjusted throughout the run to keep the acceptance rate between 25–75%.

`temp` Temperature of the simulation (default value is 300 K).

3.3.3 Subtask Run (or calc)

Signals the beginning of the Monte Carlo run. This command must be called after the `sample` and `params` subtasks have been called in the `montecarlo` section.

3.3.4 Subtask Plot

Plot the energy terms generated during a Monte Carlo run. This command must be used *after* the subtask `run`. This is a general subtask, and other plotting options are available through the standard plotting commands (see Appendix B [Plot], page 231).

`individual`
Plots all individual terms.

`group` Plot groups of energy terms.

`superimpose`
Superimposes all energy terms onto one plot. Other plot options are specified as in the main plot task.

`delay` Save plotting coordinates in a file to be plotted later on another machine. Without this, a line printer type plot will appear in the main output file.

For example

```
plot indiv delay file refine.plot
```

saves all individual energy terms in a file called `refine.plot`.

3.3.5 Subtask Save

This command is used to save the current results of a Monte Carlo simulation; If there is an unexpected end of the run, then `restart` can be used later. This must be called before `run`.

- `save file` *fname* `*`

`file` The name of the saved data (binary) file. See Section 3.3.6 [Restart (montecarlo)], page 84. Note that a `*` character is required to signify the end of the file name.

3.3.6 Subtask Restart

Restart a Monte Carlo simulation that was started and then saved previously with the `save` option. Must be called immediately preceding `run` or parameters may be over-written. It is used as in

- `restart file` *fname* `*`

where `file` directs where to find the saved data, and *fname* must be terminated with a '`*`' to signify the end of the name.

3.3.7 Subtasks Read and Write

See Section 3.1.7 [Read/write (minimize)], page 74.

3.4 Task Hybrid Monte Carlo (HMC)

The Hybrid Monte Carlo (HMC) method is often called "bad MD but good MC". Even though HMC is regarded as a Monte Carlo method, it uses Molecular Dynamics to perform the conformation-space search. Thus, in many respects, HMC's subtasks can be compared to those for Molecular Dynamics, as both usually call the same functions. Since molecular dynamics is only used for generating new conformations, a much larger time step can usually be used (this is why it is called bad MD), with the Metropolis criterion determining which moves to accept or reject.

3.4.1 HMC Methodology

The J-Walking and S-Walking methods are also implemented on the basis of the HMC protocol, and can be turned on by specifying subtasks. Since HMC performs the same simulation as does constant temperature molecular dynamics, many input controls for constant temperature MD are also suitable for HMC or are very similar for it, as you can see from the example shown below.

The following is a brief description of the S-walking (Smart Walking) method proposed by R. Zhou and B. J. Berne.[1] The S-Walking method is closely related to the J-Walking method proposed by Frantz et al.[2] Like the J-Walking method, the S-Walking method runs two walkers, one at the temperature of interest, the other at a higher temperature that more efficiently generates ergodic distributions. Instead of sampling from the Boltzmann distribution of the higher temperature walker as in J-Walking, S-Walking first approximately minimizes the structures being jumped into, and then uses the relaxed structures as the trial moves at the low temperature. By jumping into a relaxed structure, or a local minimum, the jump acceptance ratio increases dramatically. This makes the protein system easily undergo barrier-crossing events from one basin to another, thus greatly improving the ergodicity of the sampling. The method approximately preserves detailed balance provided the time between jumps is large enough to allow effective sampling of conformations in each local basin.

Here is a very simple example of a HMC calculation that uses S-Walking (more detailed examples can be found in Section C.4.4 [S-Walk (example)], page 321):

[1] *J. Chem. Phys.*, **107**, *9185* (1997)
[2] *J. Chem. Phys.* **93**, *2769* (1990)

```
HMC
   input cntl mxcyc 10000 nmdmc 5 delt 0.0015 relax 0.01 seed 101 -
         nprnt 100 tol 2.0e-7
   input cntl swalk cycgap 5000 cycrec 20 minstep 100 -
         jtemp 500.0 jrate 0.1
   input target temperature 300.0
   write trajectory coordinates and velocities every 10 -
         external file pentpep.trj
   run
   write  restart coordinates and velocities formatted file pentpep.rst
   write pdb brookhaven name pentpep file pentpep_swk.pdb
QUIT
```

3.4.2 Subtask Input

Reads in program control parameters for the HMC run.

- `input cntl mxcyc` *cycles* `[ nmdmc` *num* `] [delt` *time_step* `] -`
  `[ relax` *val*`] [ seed` *num* `] [ stop rotations ] [ nprnt` *freq* `] -`
  `[ tol` *tol* `] [metric` *value*`]`
- `input cntl [ statistics [ on | off ] ]`
- `input cntl [ swalk | jwalk ] [ cycgap` *cycles* `] [cycrec` *cycles* `] -`
  `[ jtemp` *temp* `] [ jrate` *rate* `] [ minstep` *steps* `] [metric` *num* `]`
- `input target temperature` *T_f*

HMC samples the conformation space with the canonical ensemble. Thus the underlying molecular dynamics by default is constant temperature constant volume MD. This results in coupling the system to an external heat bath with a temperature that is specified by '`target temperature`'. Note that unlike dynamics, there is no '`initialize temperature`' option for HMC. Instead, HMC initializes velocities to a distribution based on '`target temperature`' at the beginning of each HMC step.

Several parameters can be specified in the '`input cntl`' line:

`mxcyc` Number of HMC cycles to be performed.

`nmdmc` Number of MD steps per HMC cycle (5). The total number of MD steps will be equal to (mxcyc * nmdmc).

`nprnt` Number of MD steps after which contributions to the energy will be printed out (5).

`delt` Time step in picoseconds (0.001).

`relax` Relaxation time in ps for velocity scaling (if using '`constant temperature`') (0.01).

`seed` Seed to be used to start the random number generator when initializing the velocities for any species.

`tol` Tolerance to be used when applying the constraints in `SHAKE` and `RATTLE` ($1.0 \cdot 10^{-7}$).

`jwalk` Turn on the `jwalk` option. This option performs J-Walking with other parameters specified by following items. It runs an extra high-temperature walker for barrier crossing, so the total MD steps will be doubled.

`swalk` Turn on the `swalk` option. This option performs S-Walking with other parameters specified by following items. It also runs an extra high-temperature walker for barrier crossing, so the total MD steps will be doubled. The difference between `swalk` and `jwalk` is that `swalk` option performs a rough local minimization for high-temperature conformations, while the `jwalk` option does not.

`cycgap` Number of HMC cycles for the high-temperature walker or low-temperature walker before they switch (1000). The two walkers are run in tandem.

`cycrec` Number of HMC cycles between records written of the high temperature-walker's configuration (20), where cycgap/cycrec = number of records stored in file *highT.cnf*.

`jrate` Trial jump rate (1.0%).

`tempj` Jump-S/Jwalker's (high-temperature walker) temperature (500.0 K).

`minstep` Steepest decent minimization steps in S-walking (100)

`metric` Parameter for ergodicity analysis (0). metric = 1, perform ergodic metric calculation; metric = 0, no metric calculation.

`stop rotations`
Flag for stopping the center of mass motion. Default is not to stop the center of mass motion.

`statistics on`
`statistics off`
Toggles collection of statistics on the fluctuations of the different energy terms during the simulation. In earlier versions this was always on; now it is off by default.

- `input target temperature` *T_f*

Allows the specification of the final temperature (*T_f*) for the whole system. The actual temperature will fluctuate about the desired value. At each MD step the kinetic energies will be scaled so the temperature will approach the desired value on a timescale determined by the `relax` parameter.

3.4.3 Subtask Run

Performs the actual molecular dynamics run, as described in the Molecular Dynamics Run subection (see Section 3.2.2 [Run (dynamics)], page 79). The temperatures are initialized at this step, not when the values are read from the '`input cntl`' line. The user can choose among three different algorithms for the integration of the equations of motion: the Verlet algorithm, which is the default; and two based on the reversible RESPA (r-RESPA) of Tuckerman, Berne and Martyna, *J. Chem. Phys.*, **97** (1992). Currently at most three inner stages are allowed and the frequency with which the corresponding forces are updated is controlled by the parameters *freqf* (fast forces), *freqm* (medium and slow forces) and *freqs* (slow forces). Currently *freqm* and *freqs* only have meaning if the FMM (fast multipole) code is used. On the other hand, *freqf* can be used with or without the FMM since it controls only the bonding forces. If the FMM is used and *freqs* is present, the forces are separated in three pieces: those arising from nearby bodies; those arising from bodies in the first and second neighbors that are not very close, and those coming from the local expansions. If *freqs* is not present but *freqm* is, the second and third are collected together.

- `run [ verlet | rrespa fast` *freqf* `[ medium` *freqm* `[ slow` *freqs* `] ] ]`

3.4.4 Subtask Plot

- `plot [ individual | group | superimpose ] [ delay | postscript ] -`
  `file` *filename*

This command is used to `plot` the energy terms generated during a `dynamics`, `HMC` or `montecarlo` run. It must occur after subtask `run`.

`individual`
: Plot all individual terms.

`group`
: Plot groups of energy terms.

`superimpose`
: Superimpose all energy terms onto one plot.

3.4.5 Subtasks Read and Write

Read or Write a) a `restart` file containing final coordinates, and velocities (forces could also be written) or b) a `trajectory` file (see Section 3.1.7 [Read/write (minimize)], page 74).

3.4.6 Subtask Convert

This subtask is provided to ease the transition to the new, default, `external` binary format (see Section 3.1.7 [Read/write (minimize)], page 74).

- `convert -`
  `from [ unformatted | external ] file` *filename* `-`
  `to [ unformatted | external ] file` *filename* `-`
  `[ real4 | real8 | inte2 ] [ box | nobox ] -`
  `[ first` *start* `last` *end* `]`

  Reads a trajectory file written in one format and writes it out in another. The keywords `box`, `nobox`, `real8`, `real4` and `inte2` apply only to the output file and allow the user to specify the corresponding options differently from the ones used when the input file was written (see Section 3.1.7 [Read/write (minimize)], page 74). Note that `inte2` is the same as `real4` when using the `external` format.

  The parameters `start` and `end` allow the user to convert only a portion of the trajectory file. Since both input and output formats can be the same this is a handy way of extracting a consecutive sequence of frames.

3.5 Task Linear Response Method (Liaison, LRM, or LIA)

Liaison, embodied in the `LRM` or `LIA` task, is Schrödinger's implementation of the Linear Response Method (LRM), also called the Linear Interaction Approximation (LIA), a method of combining molecular mechanics calculations with experimental data to build a model scoring function for the evaluation of ligand-protein binding free energies.

3.5.1 Liaison Overview

LRM-type methods were first suggested by Aqvist (J. Aqvist, C. Medina and J. EA. Samuelsson, *Protein Eng.* **7**, 385-391, 1994; T. Hansson and J. Aqvist, *Protein Eng.* **8**, 1137-1144, 1995), based upon approximating the charging integral in the free energy perturbation formula with a mean value approach in which the integral is represented as half the sum of the values at the endpoints, namely the free and bound states of the ligand. Since then they have been pursued by a number of research groups including that of Jorgensen (D. K. Jones-Hertzog and W. L. Jorgensen, *J. Med. Chem.*, **40**, 1539-1549, 1997), who has reported very good results for a number of ligand binding data sets. From a computational standpoint, this approximation has a number of highly attractive features:

1. In contrast to free energy perturbation (FEP), where a large number of intermediate *windows* must be evaluated, the LIA requires simulations of only the ligand in solution and the ligand bound to the protein. The idea is that one views the binding event as a replacement of the aqueous environment of the ligand with a mixed aqueous/protein environment.
2. Again in contrast to FEP, one can study disparate ligands as long as they have similar binding modes. FEP allows only very small changes between ligands to be investigated; the differences in the data sets we have examined up to this point are much more significant.
3. Only interactions between the ligand and either the protein or the aqueous environment enter into the quantities that are accumulated during the simulation; the ligand-ligand, protein-protein and protein-water interactions are part of the "reference" Hamiltonian and hence are used to generate configurations in the simulation (via either Monte Carlo or molecular dynamics) but are not used as descriptors in the resulting model for the binding free energy (see below). This eliminates a considerable amount of noise and systematic uncertainties in the calculations, for example arising from different conformations of the protein obtained from cocrystallized structures of different ligands.
4. The method as implemented by Jorgensen et al. contains three terms in the empirical formula for the binding energy: electrostatic, van der Waals, and solvent accesible surface area (SASA):

$$\Delta G = \alpha(\langle U^b_{elec}\rangle - \langle U^f_{elec}\rangle) + \beta(\langle U^b_{vdw}\rangle - \langle U^f_{vdw}\rangle) + \gamma(\langle U^b_{SASA}\rangle - \langle U^f_{SASA}\rangle)$$

$\langle ... \rangle$ means ensemble average from a Monte Carlo or Molecular Dynamics simulation, and all terms are evaluated only for interactions between ligand and its "environment". Aqvist et al. used only two terms in their original work, i.e., electrostatic and van der Waals interaction. However, Jorgensen et al. found that it is necessary to add one more term for larger data sets, and the third term was also proposed to be just a constant term. In our implementation as discussed later, the third term is based on the cavity energy in the SGB continuum solvent model.

If the linear response approximation was rigorously valid, the coefficient of the electrostatic term would be 0.5, corresponding to the mean value approximation to the charging integral. In fact, one can recover a value very close to this for less complex systems, such as solvation of small molecules in water. However, some of the steps involved in the binding event, such as the removal of water from the protein cavity and subsequent introduction of the ligand, are unlikely to be accurately described by a linear model. Therefore, in practice, optimization of fitting parameters yields electrostatic coefficients that are significantly different from the ideal value of 0.5. By allowing this empirical element, one is sacrificing generality; the method probably requires that the ligands have similar binding modes, and new parameters must be developed for each receptor. In return, however, one can obtain a reasonable level of accuracy (reflected in cross-validation studies as well as the overall fitting accuracy) with a modest expenditure of CPU time, under assumptions that are quite reasonable for many structure-based drug design projects.

We have developed an implementation of the LIA, in the context of the Impact program, using the generalized Born continuum solvation model and the OPLS-AA force field of Jorgensen and coworkers. To our knowledge, this is the first commercially available version of the LIA and the first version of any type to utilize continuum solvation. Key features of the Schrödinger implementation are as follows:

1. First, we replaced the solvent accessible surface area term in Jorgensen's LIA formulation by the cavity term in the continuum solvent model:

$$\Delta G = \alpha(\langle U^b_{elec}\rangle - \langle U^f_{elec}\rangle) + \beta(\langle U^b_{vdw}\rangle - \langle U^f_{vdw}\rangle) + \gamma(\langle U^b_{cav}\rangle - \langle U^f_{cav}\rangle).$$

   We think it makes sense to use such a term in the context of a continuum solvent model. Indeed, it is not clear why the solvent accessible surface area is needed in an explicit solvent model, since waters are explicitly represented already.

2. The use of a continuum model provides much more rapid convergence of the simulations. The statistics on the various interaction terms are significantly better converged than in an explicit solvent simulation, and the required CPU time is much smaller.
3. We have implemented an automatic atom typing scheme for the OPLS-AA force field that assigns charges, van der Waals, and valence parameters with no human intervention. A key feature of OPLS-AA is excellent reproduction of condensed phase properties, obtained via fitting to liquid state simulations. Over the past years Jorgensen and coworkers have rapidly extended the functional-group coverage of OPLS-AA to include a larger number of pharmaceutically relevant species. This work will be continued and expanded at Schrödinger and at Columbia University (Prof. Richard Friesner) in collaboration with Professor Jorgensen. We intend in the coming year to increase both the accuracy and coverage of OPLS-AA substantially.
4. The Maestro interface to Liaison produces scripts that allow a series of Liaison jobs to be run automatically. This makes it convenient to use the method in the context of an industrial structure-based drug design effort, in which a large number of molecules need to be examined.

Here is a very simple LRM example that uses the SGB continuum solvent model (more detailed examples can be found in Section C.4.5 [Liaison (example)], page 322):

```
LRM
 assign ligand name drug
 input cntl average every 10 file lrm_bound.ave
 sample dynamics
 input cntl nstep 10000 delt 0.001 relax 0.01 nprnt 100 seed 101 -
   constant temperature
 input target temperature 300.0
 run rrespa fast 2
 write restart coordinates and velocities formatted file cmpx_lrm.rst
 write pdb brookhaven name prot file prot_lrm.pdb
 write pdb brookhaven name drug file lig_lrm.pdb
QUIT
```

3.5.2 Subtask Assign

Specifies the LRM or LIA ligand in the LRM simulation. This *ligand* can in fact be any entity; it could be a single ligand, a pair of ligands from a ternary complex, or even a protein, as long as all the components reside in a single species.

- `assign ligand name` *spec*

`name` *spec* determines the LRM ligand. The program thus will calculate and collect all interactions between this ligand and its "environment" (protein or water), but not the interactions within ligand itself or the protein (water) itself. In the continuum solvent model, this means that we need to separate the single and pairwise energies in the Generalized Born model into proper partial contributions to represent the LIA interaction between ligand and protein.

3.5.3 Subtask Param

Specifies LRM or LIA parameters, i.e., α, β, γ in the LRM simulation.

- `param elec` *val* `vdw` *val* `cavity` *val*

As mentioned above, the current method requires that new parameters be developed for each receptor, so this option is not actually used at present. Schrödinger's Maestro user interface generates scripts, as described below, that automate the LRM simulations on various ligands with known binding energies, and perform the requisite data collection. Then the user can run another script to calculate the LRM parameters and report the goodness of the fit to the experimental binding energies. Finally, the user can apply these parameters to predict the binding energies of new systems.

3.5.4 Subtask Input

Reads in program control parameters for the LRM simulation.

- `input cntl average every` *num* `file` *filename*

This command controls options for collection of the LRM statistics. It specifies how often the average LRM interaction energies are to be calculated and which file to use to print out the ensemble averages. (Other LRM-specific options may also be specifiable here in the future.)

`every`	Calculate the LRM ensemble average every *num* steps.
`file`	Write out the ensemble averages to file *filename*.

3.5.5 Subtask Sample

Selects a sampling method for the LRM simulation, such as Molecular Dynamics or Hybrid Monte Carlo.

- `sample [ dynamics | HMC ]`

The commands that follow the choice of sampling method are identical to those that would be needed if that method were invoked as a standalone task. This is illustrated in the previous example, where `dynamics` was chosen as the sampling method; all commands after `dynamics` are identical to those expected for the `dynamics` task. The following example uses `HMC` as the sampling method:

```
LRM
 assign ligand name drug
 input cntl average every 10 file lrm_bound.ave
 sample HMC
 input cntl mxcyc 10000 nmdmc 5 delt 0.0015 relax 0.01 seed 101 -
       nprnt 100 tol 2.0e-7
 input cntl swalk cycgap 5000 cycrec 20 minstep 100 -
       jtemp 500.0 jrate 0.1
 input target temperature 300.0
 run
 write restart coordinates and velocities formatted file cmpx_lrm.rst
 write pdb brookhaven name prot file prot_lrm.pdb
 write pdb brookhaven name drug file lig_lrm.pdb
QUIT
```

3.5.6 Scripts for Liaison simulation and fitting

Because generating fitting data for Liaison typically involves running similar simulations on a number of different systems (the *training set*), we recommend setting up these simulations, and the parameter-fitting job based on their results, from the Maestro user interface. (See the *FirstDiscovery Quick Start Guide* for examples of setting up such jobs.) To set up a Liaison simulation job from Maestro, it is necessary to provide an overall job name and the structures that constitute the training set, which may be one receptor and several ligands. Under the *current working directory* (CWD) from which you run Maestro, it sets up a directory with the overall job name ('`fit_lia`' in the following example), and a subdirectory under that for each ligand structure in the training set ('`pose1_H15`', etc.):

```
hal9000% ls -l
total 912
-rw-r--r--    1 banks    glidegrp     119 Jul 20 11:19 bindE.expt
-rwxr-xr-x    1 banks    glidegrp     374 Jul 20 11:19 change_sgbparam_fit_lia*
-rwxr-xr-x    1 banks    glidegrp     312 Jul 20 11:19 fit_fit_lia*
drwxr-xr-x    7 banks    glidegrp     116 Sep 10 10:27 fit_lia/
-rw-r--r--    1 banks    glidegrp  430687 Jul 20 11:19 fit_lia.mae
-rw-r--r--    1 banks    glidegrp    1170 Jul 20 11:19 liafit_fit_lia.out
-rwxr-xr-x    1 banks    glidegrp     452 Jul 20 11:19 simulate_fit_lia*
```

```
hal9000% ls -l fit_lia
total 64
drwxr-xr-x    2 banks    glidegrp    4096 Sep 10 10:27 pose1_H15/
drwxr-xr-x    2 banks    glidegrp    4096 Sep 10 10:27 pose2_H16/
drwxr-xr-x    2 banks    glidegrp    4096 Sep 10 10:27 pose3_H17/
drwxr-xr-x    2 banks    glidegrp    4096 Sep 10 10:27 pose4_H12/
drwxr-xr-x    2 banks    glidegrp    4096 Sep 10 10:27 pose5_H11/
hal9000% ls -l fit_lia/pose1_H15
total 1864
-rw-r--r--    1 banks    glidegrp    1170 Jul 20 11:19 bound.inp
-rw-r--r--    1 banks    glidegrp     799 Jul 20 11:19 free.inp
-rw-r--r--    1 banks    glidegrp     558 Jul 20 11:19 pose1_H15.bound.ave
-rw-r--r--    1 banks    glidegrp   12979 Jul 20 11:19 pose1_H15.bound.log
-rw-r--r--    1 banks    glidegrp   33587 Jul 20 11:19 pose1_H15.bound.out
-rw-r--r--    1 banks    glidegrp     186 Jul 20 11:19 pose1_H15.free.ave
-rw-r--r--    1 banks    glidegrp   12205 Jul 20 11:19 pose1_H15.free.log
-rw-r--r--    1 banks    glidegrp   35752 Jul 20 11:19 pose1_H15.free.out
-rw-r--r--    1 banks    glidegrp   10167 Jul 20 11:19 pose1_H15_lig.mae
-rw-r--r--    1 banks    glidegrp    9059 Jul 20 11:19 pose1_H15_lig_min.mae
-rw-r--r--    1 banks    glidegrp  430687 Jul 20 11:19 pose1_H15_rec.mae
-rw-r--r--    1 banks    glidegrp  363077 Jul 20 11:19 pose1_H15_rec_min.mae
```

In each of the ligand subdirectories, Maestro sets up simulation jobs for that ligand alone ('`free.inp`'), and the ligand-receptor complex ('`bound.inp`'), whose results give the energy terms in the LIA expression for ΔG above, for which the α, β, and γ coefficients are then fit to experimental binding energies for the systems in the training set. The command script `simulate_`*jobname* (in this case `simulate_fit_lia`) runs the simulations in each directory (either sequentially, or if the user specifies multiple processors, in parallel on the available processors), and renames the output files by prepending the name of each ligand, e.g. '`pose1_H15.bound.log`'.

For the parameter-fitting component of Liaison, Maestro sets up the script `fit_`*jobname*, which runs a least-squares fitting program to fit the output of the simulations to experimental data, which it reads from the file '`bindE.expt`' in this case. The fitting program prints its output to the file '`liafit_`*jobname*`.out`'. (Headers, ligand names, and intercolumn spaces are abridged here to fit on the page.)

```
Input energy components:
Ligand   vdw_f  coul_f   rxn_f   cav_f   vdw_b  coul_b   rxn_b   cav_b    Expt
1_H15    0.000   0.000 -29.979   3.775 -51.264 -23.280   6.290   1.104  -9.350
2_H16    0.000   0.000 -30.520   3.941 -51.035 -27.165   1.046   1.095 -11.190
3_H17    0.000   0.000 -23.622   3.959 -56.821 -26.490   9.024   1.095 -12.160
4_H12    0.000   0.000 -25.415   3.735 -50.892 -17.000  -6.610   1.093  -9.930
5_H11    0.000   0.000 -18.047   3.756 -56.033 -16.753  -1.967   1.094 -11.890
```

```
Liaison SVD-fitted parameters: alpha*Dvdw + beta*Delec + gamma*Dcav:
alpha =     0.145880   +-   0.018366
beta  =     0.031038   +-   0.004276
gamma =     1.517949   +-   0.383891

Chi-square:   202.172089

Binding energies fitted by SVD:
Ligand-Name     SVD-Fitted   Experiment
pose1_H15          -10.005       -9.350
pose2_H16          -10.648      -11.190
pose3_H17          -11.433      -12.160
pose4_H12          -10.795       -9.930
pose5_H11          -11.737      -11.890

RMSD error for binding energies =   0.636
```

3.5.7 Scripts for Liaison binding energy prediction

After fitting the LRM coefficients to experimental data for the training set, predicting binding energies for one or more new systems is a simple matter of running simulations on the new systems (bound and free, as for the training set) to obtain the required energy terms, which are then multiplied by the fit coefficients. In a prediction job, the Maestro interface sets up a script to run the simulations, again called `simulate_`*jobname*, in the *jobname* directory, where *jobname* may be different from that for the simulations on the training set. (If it's the same, the result will be to overwrite the previous `simulate_` *jobname* script, but there may be advantages to keeping both the training set and the predicted set under the same *jobname* directory. Here we use the job name `predict_lia` for the prediction run.) Maestro also sets up the script `predict_`*jobname* to calculate the predicted binding energies of one or more new ligands, using coefficients obtained from the previous fitting job. The following example is for a single ligand.

```
hal9000% ls -l
-rwxr-xr-x    1 banks         382 Jul 20 11:19 change_sgbparam_predict_lia*
-rw-r--r--    1 banks         310 Jul 20 11:19 liapredict_predict_lia.out
drwxr-xr-x    3 banks          54 Sep 10 10:27 predict_lia/
-rw-r--r--    1 banks      374748 Jul 20 11:19 predict_lia.mae
-rwxr-xr-x    1 banks         498 Jul 20 11:19 predict_predict_lia*
-rwxr-xr-x    1 banks         426 Jul 20 11:19 simulate_predict_lia*
hal9000% ls -l predict_lia
drwxr-xr-x    2 banks        4096 Sep 10 10:27 H06_altered_predict/
```

```
hal9000% ls -l predict_lia/H06_altered_predict
-rw-r--r--    1 banks         558 Jul 20 11:19 H06_altered_predict.bound.ave
-rw-r--r--    1 banks       13245 Jul 20 11:19 H06_altered_predict.bound.log
-rw-r--r--    1 banks       33572 Jul 20 11:19 H06_altered_predict.bound.out
-rw-r--r--    1 banks         186 Jul 20 11:19 H06_altered_predict.free.ave
-rw-r--r--    1 banks       11883 Jul 20 11:19 H06_altered_predict.free.log
-rw-r--r--    1 banks       30762 Jul 20 11:19 H06_altered_predict.free.out
-rw-r--r--    1 banks      374748 Jul 20 11:19 H06_altered_predict_lig.mae
-rw-r--r--    1 banks       10327 Jul 20 11:19 H06_altered_predict_lig_min.mae
-rw-r--r--    1 banks      374748 Jul 20 11:19 H06_altered_predict_rec.mae
-rw-r--r--    1 banks      364939 Jul 20 11:19 H06_altered_predict_rec_min.mae
-rw-r--r--    1 banks        1228 Jul 20 11:19 bound.inp
-rw-r--r--    1 banks         819 Jul 20 11:19 free.inp
```

The prediction script `predict_`*jobname* writes its output to the file '`liapredict_`*jobname*`.out`':

```
LIA prediction: predict_lia

Input data:
Van der Waals term coefficient (alpha) : 0.14588
Electrostatic term coefficient (beta)  : 0.031038
Cavity term coefficient (gamma)        : 1.51795

Calculated results:
Ligand-Name               Binding Energy (Kcal/mol)
H06_altered_predict              -12.780
```

3.6 Task Docking (DOCK or GLIDE)

The DOCK task, also called Glide (for Grid-based LIgand Docking with Energetics), is the heart of Schrödinger's Glide product. The docking algorithm searches for favorable interactions between a (typically) small ligand molecule and a (typically) larger receptor molecule, usually a protein. The ligand and receptor typically occupy separate Impact species, though they may also be separate molecules in the same species. The ligand must be a single Impact molecule, while the receptor may include more than one molecule, e.g. a protein and a cofactor. Because of the relative complexity of this task, several examples of its use are included in this section, in addition to the usual meta-examples under each subtask or command. Another example may be found in Section C.4.8 [Glide (example)], page 330.

3.6.1 Description of the Docking Algorithm

The docking procedure for a given ligand molecule runs through two stages, which we refer to as *rough scoring* and *grid energy optimization*. Each stage relies on grids representing the receptor binding site, but the grids for one stage are not the same as for the other. As in other docking programs such as DOCK (E.C. Meng, B.K. Shoichet and I.D. Kuntz, *J. Comput. Chem.* **13**, 505, 1992) and Autodock (G.M. Morris, D.S. Goodsell, R.S. Halliday, R. Huey, W.E. Hart, R.K. Belew and A.J. Olson, *J. Comput. Chem.* **19**, 1639, 1998), the grids can be precomputed and stored on disk, so it is unnecessary to read in the receptor molecule, and perform computations on it, repeatedly for multiple ligands or multiple conformers of the same ligand. Using grids also makes computing the ligand-receptor interaction energy an $O(nlig)$ rather than $O(nlig * nprot)$ process, where *nlig* is the number of atoms in the ligand and *nprot* is the number of atoms in the receptor.

In a typical project, the user will set up the grids in one Glide run, and dock ligands in one or more subsequent runs, as described below. It is not currently possible to set up grids and dock ligands in the same run. (See "Important Operational Notes" in the *FirstDiscovery Technical Notes*.) In all cases, the user should specify saving the grids to disk whenever calculating them.

In the current version of Glide, there are two possible ways to incorporate ligand flexibility: include multiple conformers of a given ligand in the input to Impact, or use the program's internal conformation generator starting with a single conformer of a given ligand. We strongly recommend the latter. It covers conformational space systematically, and by clustering conformers that have a common "core," it runs much faster than docking the same number of externally generated conformers. In conjunction with internal conformation generation, Glide also allows ligand torsional flexibility during the optimization of the ligand-receptor interaction energy, and we

recommend using this feature. Future versions of Glide will allow for receptor flexibility; for now, scaling of the van der Waals radii of receptor atoms (also available for ligand atoms) mimics some possible motions of the receptor, such as "breathing" to fit a larger ligand than the one present in a particular co-crystallized structure.

In addition to generating or processing multiple conformations of a given molecule, Glide can also dock, and compare the predicted binding affinities of, multiple ligand molecules in a single Impact run, using a loop in the input scripting language (DICE). In the case of externally generated conformers, the same loop can run over a list of input structures that includes both different molecules and different conformers of each, using Impact's `build primary check` syntax to determine which is which. (The input structures for internal conformation generation can in principle also include multiple conformers of the same ligand, but there is no reason to do so, and we do not recommend it.)

The first stage of the algorithm, known as *screening* or *rough scoring*, measures the geometric "fit" between the ligand and receptor molecules, and approximations to specific interactions between them such as hydrogen bonds. The grids for the rough-scoring stage contain values of a *rough score function* representing how favorable or unfavorable it would be to place ligand atoms of given general types (e.g. polar hydrogens, hydrogen bond acceptors, hydrophobic heavy atoms) in given elementary cubes of the grid. These grids have a constant spacing, which defaults to 1 Å. The *rough score* for a given *pose* (position and orientation) of the ligand relative to the receptor is simply the sum of the appropriate grid scores for each of its atoms. By analogy with energy, favorable scores are negative, and the lower (more negative) the better.

The screening stage is actually a hierarchical series of filters that drastically narrow down the set of poses that are considered candidates for docking. A given pose is defined by three Cartesian coordinates of the ligand *center*, and three Euler angles. The ligand center is taken to be the midpoint of the *diameter*, which in turn is taken to be the longest line segment connecting two ligand atoms. Although some of the commands in the docking task use the abbreviation `cm` in keywords to refer to this point, this definition is very different from the *centroid* or "center of mass" of the ligand atom positions. Note also that it may be far from the actual position of any ligand atom. (In fact, if the ligand "wraps around" a convex portion of the receptor surface, the ligand center may be inside the receptor.) The Cartesian coordinates of the center position are defined relative to the origin of coordinates in the receptor coordinate file. The Euler angles ψ and θ are defined relative to an orientation in which the ligand diameter points along the z-axis; the ϕ angle (rotation of the ligand about its diameter) is taken to be zero in the input coordinates of the ligand. This biases one of the six coordinates in favor of its input value, but we have not found this to be a problem even when the

input is the "correct answer", e.g., a co-crystallized ligand-receptor complex. It is also possible to choose the grid points to include the ligand center coordinates in the input, which introduces additional bias. The ligand poses that constitute the search space for the screening step correspond to discrete values of these six coordinates. The ligand center is placed at selected points on the rough-score grid, with the default being every other point. The ψ and θ angles are taken from the polar coordinates of a set of points uniformly distributed on the unit sphere (by default, a set of 302 such points from the file '`grid.pts`'), and ϕ is distributed evenly between 0 and 360 degrees, with the default being 25 values at intervals of 14.4 degrees.

Early filters in the screening stage are purely geometric, weeding out sites for the ligand center that have no chance of being good docking positions, because they are too far from the receptor or have no chance of shape complementarity. The later filters involve evaluating the rough-score function on subsets of the ligand atoms, such as those near the diameter (whose scores should be independent of ϕ, so ruling them out for one value of ϕ kills 25 poses based on as few as 2 ligand atoms), or hydrogen-bonding atoms (or others expected to make major contributions to favorable scores, so that if the score is not favorable for the subset, there's no point in evaluating it for the rest of the ligand). Effective application of the filters can rapidly reduce the number of poses to be considered from hundreds of thousands or millions to a few dozen (or less), before evaluating the full rough-score function on all the ligand atoms in any pose.

By default, and by our recommendation, the rough-scoring function is defined on a 1 Å grid. In the interest of execution speed, the default sites for the ligand center occupy a 2 Å grid consisting of alternating points of the rough-score grid. The default rough-score function is based on counting receptor atoms of various types within certain distances of grid points, and thus has a step-function character, and can vary considerably from one grid point to the next. Therefore a pose that gets an unfavorable score may be very close in space to one that would get a favorable score, and possibly would minimize to a good docked configuration. If the favorable score occurs for a pose with the ligand center on a skipped grid point, it might never be found. This is particularly likely for receptors with tight binding pockets.

To address this potential problem, Glide allows two enhancements of the rough-score function, which we call *greedy scoring* and *pose refinement*. Both involve examining scores at grid points surrounding the current positions of ligand atoms, but avoid the considerable expense of moving every atom of every pose through a 3x3x3 set of neighboring points.

Greedy scoring involves setting up alternative rough-score grids, which at each grid point incorporate some "influence" of the most favorable score in the 3x3x3 neighborhood of the central grid point. To construct a "greedy grid" given the original rough-score grid, the algorithm first finds the most favorable (lowest or most negative) score in the 3x3x3 neighborhood. The

value stored in the greedy grid at the given grid point is then a linear combination of the original grid value and the best neighboring one: greedy = x * best + $(1-x)$ * original. The default is $x = 0.33$, but the user may specify any value between 0 (the same as non-greedy scoring) and 1, inclusive.

Pose refinement is a method for evaluating the rough-scores of selected poses on a finer translational grid than the default. The refinement step takes each pose that passed all the screening tests, and moves the ligand center to neighboring grid points. The default step size for these moves is one grid point (1 Å), which with the default spacing of ligand center sites means that all the poses it covers other than the central one were skipped in the original search. If any of these "refined" poses gets a better score than the original (central) one, the algorithm passes the best such pose on to subsequent steps, instead of the central one.

Greedy scoring adds computational overhead for reading (and the first time, computing and writing) the greedy grid, and also, in our tests, about 10–20% to the CPU time for screening poses of a given conformation (presumably because more poses pass some of the filters). Pose refinement adds a negligible amount of time to a multiple-conformation or multiple-ligand run, and tends to *decrease* the number of poses that need to be passed to minimization. Because they significantly enhance the likelihood of finding good poses, we recommend using both features.

In a run with multiple externally-generated conformations of a given ligand, the program executes most efficiently (in both time and memory use) if it performs the (greedy) rough-score calculation for all the conformers first, keeps some specified total number of best poses over all the conformers, and then proceeds to pose refinement (and subsequent steps) only on those best overall poses of the given ligand. For internal conformation generation, the rough-scoring algorithm treats all the conformers for a given input ligand in tandem, so it automatically does pose refinement only on the best poses over all conformers.

The second stage of the docking algorithm begins with evaluation and minimization of a grid approximation to the nonbonded interaction energy between the ligand and the receptor. The grids store the values of the electrostatic potential due to the receptor atoms (with a constant or linear dielectric, at user option), and the attractive and repulsive parts of the Lennard-Jones energy. The docking algorithm is implemented only for the OPLS-AA force field. Attempting to use it with a different force field will result in an error exit from Impact.

The energy values are defined on an *adaptive* grid, with a finer spacing close to the receptor for accuracy where the potential energy is changing rapidly, and coarser far from the receptor to save time and space where the potential varies slowly (and contributes less to the total in any case). The default for the finest grid spacing is 0.4 Å, increasing to 3.2 Å in three steps. At user option, the grid energy also incorporates *smoothing functions* that eliminate

the singularity in the potential energy at zero distance, and thus soften the hard walls that could otherwise trap the algorithm in local minima. We recommend starting the grid-energy minimization on the smoothed potential surface, and *annealing* to the full OPLS-AA grid energy. To accomplish this, include the subtask `smooth anneal 2` in the `DOCK` task.

The energy evaluations and minimizations use a continuous function for the energy, obtained by linear interpolation among the values at the corners of the cube of grid points surrounding each ligand atom position. The position and orientation coordinates of the ligand are varied continuously during the minimization. With Glide's internal conformation generation feature, we also provide, and recommend, the option of varying ligand dihedral angles during the minimization.

Glide performs its calculations in the context of two concentric rectangular boxes, representing different aspects of the receptor active site. The *bounding box* (or "ligand center box") delimits the space in which the ligand center (as defined above) can move. The size of this box determines the size of the space that the algorithm explores, and thus the amount of computer time (and to some extent memory) it takes to execute, so to optimize performance, it should be as small as the user's knowledge of the binding site will allow. Around this bounding box, the *enclosing box* is the space in which Glide defines and calculates the grid values for the rough-score and energy functions. The algorithm rejects a candidate site for the ligand center if any conformation and pose of the ligand, with its center at that site, would have any atom outside the enclosing box. Therefore it is important to make the enclosing box large enough relative to the bounding box so that the ligand will fit inside it at all likely sites for its center. Memory restrictions, unfortunately, limit the size of the enclosing box to 50 Å on a side.

The location and dimensions of the bounding and enclosing boxes are either calculated from the coordinates of the receptor atoms in residues that the user specifies as `active`, taken directly from user specifications via the `box` keyword in the `receptor` and/or `screen` subtasks, or read from grid files previously stored to disk.

3.6.2 Example 1: Set up grids

The following example sets up grids based on the receptor in the co-crystallized thrombin-inhibitor complex contained in PDB entry 1ETS. Subsequent examples dock ligands to this receptor, as represented by these grids. In the text accompanying these examples, we briefly explain the subtasks of the `DOCK` task. In later sections devoted to each subtask, we provide more detailed descriptions, and information about overriding defaults for parameters or options not shown here. It is important to note that all of the subtasks except `confgen`, `simil`, and `run` simply set up the specifications and parameters for the docking run; except for `confgen`, which immediately

generates conformations, and `simil`, which immediately generates or reads similarity weights, Impact does not perform any docking calculations until it encounters `run`. Thus every invocation of the `DOCK` task must end with the `run` subtask. Note also that every subtask of this task occupies a single *logical line* of the Impact input file. Thus it is crucial to include the hyphens to indicate continuation of the command (subtask) on the next physical line. Furthermore, it is important to remember that each *physical* line of the Impact input file is truncated after 132 characters. For this reason, all file names in the examples shown here are on separate physical lines (with hyphens for continuation as needed). Users must insure that all their file pathnames (including directories) are short enough to fit in this limit, which typically means 128 or 130 characters in order to leave room for quotation marks and/or hyphens. The Maestro user interface will refuse to write an Impact input file, or start the corresponding job, if the user specifies a pathname that is too long. We recommend that users who have complicated directory structures should either run Impact in directories close to where their files are located, or if this is not practical, use such `Unix` system features as symbolic links or environment variables to shorten the names to be written to the Impact input file.

It will be noted that unlike most Impact input files, none of the examples in this section contains a `setmodel` task. This is because Glide computes energies differently from other tasks such as `minimize` and `dynamics`. It does so by precomputing receptor grids using the OPLS-AA force field, and reading (and interpolating) energies from them for ligand atoms, rather than looping over atom pairs. For this reason, this task does not require `setmodel` to specify features and parameters of the energy function.

```
write file "1ets_single_grid.out" -
      title "1ets_single_grid" *

CREATE
  build primary name recep type auto -
    read maestro file -
"1ets_single_grid.mae" -
    tag REC_
  build types name recep
QUIT

DOCK
  smooth anneal 2
  receptor name recep -
   writef -
"1ets_single_grid" -
   protvdwscale factor 0.900000 ccut 0.250000 -
   box center read xcent -37.510494 ycent -28.946030 zcent 44.411289 -
   boxxrange 27.346889 boxyrange 27.346889 boxzrange 27.346889 -
   actxrange 27.346889 actyrange 27.346889 actzrange 27.346889
  screen greedy -
   box center read xcent -37.510494 ycent -28.946030 zcent 44.411289 -
   ligxrange 12.000000 ligyrange 12.000000 ligzrange 12.000000 -
   writescreen -
"1ets_single_grid.save" -
   writegreed -
"1ets_single_grid_greedy.save"
  parameter clean
  final glidescore
  run
QUIT

END
```

`smooth` Indicates that the calculation of the energy grids should incorporate short-distance smoothing functions. `anneal 2` indicates that the grids should include two different potential-energy surfaces, one with smoothing and one without. In a `DOCK` task to do grid-energy optimization, `smooth anneal 2` means that the optimization should start on the smoothed surface and end on the unsmoothed one. Alternatively, a subsequent `DOCK` task could include `smooth anneal 1` to use only the smoothed surface, or omit the `smooth` subtask in order to use only the unsmoothed

surface; but we strongly recommend using `smooth anneal 2` in all cases.

`receptor` Specifies the receptor molecule(s) and its active site.

`name recep`
: Indicates that the receptor is in the Impact species designated `recep` in the preceding `CREATE` task. If this species contained more than one molecule, then by default the receptor would include all molecules in the species; specifying `mole` *mol* in this subtask would restrict the receptor to that single molecule.

`writef 1ets_single_grid`
: Indicates that the energy grids will be written to files whose names are built from the base `1ets_single_grid`. Specifically, '`1ets_single_grid.grd`' will contain structural information about the adaptive grid itself (size and coordinates of each grid box), '`1ets_single_grid_vdw.fld`' will contain the Lennard-Jones energy grid, '`1ets_single_grid_coul.fld`' will contain the Coulomb potential with a dielectric constant of 1, and '`1ets_single_grid_coul2.fld`' will contain the Coulomb potential with a distance-dependent dielectric of $1 * r$. In addition, Impact will write the receptor structure to a Maestro format file, '`1ets_single_grid_recep.mae`', for use in subsequent Glide jobs. (To compute and write just one of the Coulomb files and not the other, use the keyword `writecdie` for the constant dielectric or `writerdie` for the r-dependent dielectric. `writerdie` overrides `writecdie`, so if you specify both, only the r-dielectric will be computed and written. To specify a dielectric other than 1 or $1*r$, use the `dielco` keyword in the `minimize` subtask.) NOTE: The files read and written by Glide can be very large (tens of megabytes). To save space on user disks, and also to save time (network latency) in environments where the user disk is on a server other than the local CPU, we recommend reading and writing these files on local "scratch" disks while running Impact, and transferring them to more "permanent" locations separately.

`protvdwscale`
: Specifies a scale factor (`factor`) for the van der Waals radii of nonpolar receptor atoms. All atoms whose partial charge (absolute value) is less than `ccut` are considered nonpolar for this purpose. Specifying `factor` < 1.0, by effectively making receptor atoms seem smaller to ligands, is a way of letting the receptor "breathe" to accommodate larger ligands than the one that happened to be in the cocrystalized complex from which the receptor structure was taken. Omitting this keyword will result in no scaling (equivalent to `factor 1.0`), but we recommend using some scaling factor such as 0.9 (which the Maestro interface writes to input files). See the FirstDiscovery Technical Notes for further discussion of vdW scaling factors.

`box`
: Specifies the rectangular (in this case cubic) box in which the rough-score and energy grids are defined. (This is sometimes called the *enclosing box*). `center read` indicates that the coordinates (in Angstroms) of the center of the box are given by the following `xcent` *val* `ycent` *val* `zcent` *val* keyword-value pairs. `boxxrange` *val*, etc., give the lengths (in Angstroms) of the box edges, which are always parallel to the coordinate axes. The rough-scoring algorithm rejects a ligand center site if *any* orientation of the ligand at that site would have any atoms outside the grid box, so it is important to make `boxxrange` large enough so as not to exclude any ligand positions that may be desirable with some orientations of the ligand but outside the box with others. If `actxrange`, etc., are specified, they indicate that any residues with any atoms in a box of that size (and the given center) are counted as contributing to the receptor *surface*, a set of points on the van der Waals surface of the specified atoms, which is used to determine distances of grid points or boxes from the receptor. We strongly recommend `actxrange` = `boxxrange`, etc., but problems with the surface-generation algorithm require `actxrange`, etc., no greater than 50.0. In such cases it is acceptable to use `boxxrange > actxrange`, etc., but in fact `boxxrange >` 50.0 is probably not

necessary except for unusually large ligands or broad binding regions.

`screen` Requests the rough-score screening phase of the calculation (in this case, just setting up the rough-score grids), and specifies parameters for its performance.

`greedy` Use the greedy-scoring algorithm.

`box` Specifies the box in which the ligand center is moved. (Sometimes called the *bounding box*.) As in the `receptor` subtask, `center read` indicates that the coordinates of the box center are to be read from the following specification. In order to leave equal space for ligand atoms on all sides of the bounding box, its center should be the same as that of the "enclosing box" specified in the `receptor` subtask; but for historical reasons, Impact will accept specification of different centers for the two boxes. `ligxrange 12.0 ligyrange 12.0 ligzrange 12.0` indicates that the ligand center should move in a box of dimensions 12 Å on a side (i.e., 6 Å in each positive and negative direction from the center of the box).

`writescreen`
Write the rough-score grids to the indicated file.

`writegreed`
Write the greedy-score grids to the indicated file.

`parameter`
This subtask specifies various general parameters and conditions for running the `DOCK` task. `clean` tells Impact to delete various dynamically-allocated arrays after the task is completed. If there were subsequent `DOCK` tasks in this job, they would need the data stored in those arrays, so `clean` would not appear here.

`final` Specifies the "final" scoring function that Glide is to use for ranking ligands. `glidescore` indicates Schrödinger's proprietary *GlideScore* (tm) scoring function, adapted from the ChemScore function found in the literature.[1] `noglidescore` would indicate using just the minimized grid energy (Coulomb + vdW), which in general is inadequate for comparing different ligand molecules. The `final glidescore` subtask is needed here, even though this

[1] Eldridge et al. *J. Comput. Aided Mol. Design*, **11** p. 425–445, 1997

task does not dock any ligands, because GlideScore requires information about the receptor molecule that may not be available in the actual docking task. Glide writes this information to a file called *basename*`.csc`, where *basename* is the name specified with `receptor writef`, in this case `1ets_single_grid`.

`run`

Run the calculation. The output consists of the grid and receptor data files, for use in subsequent docking tasks or jobs. In this case, they will be '`1ets_single_grid.grd`', '`1ets_single_coul.fld`', '`1ets_single_grid_coul2.fld`', '`1ets_single_grid_vdw.fld`', '`1ets_single_grid.save`', '`1ets_single_grid_greedy.save`', '`1ets_single_grid_recep.mae`' (receptor data for use by the `report` subtask in a subsequent job or `DOCK` task), and '`1ets_single_grid.csc`'. The '`.grd`' and '`.fld`' files are binary, the rest are ASCII.

3.6.3 Example 2: Single Ligand, Single Conformation

The following example uses the receptor data and grid files that the previous one wrote, to dock a single ligand, which happens to be the cocrystallized ligand from the same "1ets" thrombin-inhibitor complex as the receptor. This example shows rigid docking of a single conformation of the ligand. The next (multi-ligand) example will show internal conformation generation, and torsional flexibility in the energy optimization stage.

This example contains four different `DOCK` tasks, for different stages of the calculation. Some of these could be combined for this particular run, but are separated either because that's the way they would appear in a multi-ligand run (some within a `WHILE` loop, others outside it), or in order to illustrate different options for the commands included in the `DOCK` task.

```
write file "1ets_single_dock.out" -
      title "1ets_single_dock" *

DOCK
  smooth anneal 2
  receptor rdiel readf -
"1ets_single_grid"
  screen readscreen -
"1ets_single_grid.save" -
   greedy readgreed -
"1ets_single_grid_greedy.save" -
   maxkeep 1000 scorecut 100.000000
  ligand multiple maxat 100 maxrot 15 -
   ligvdwscale factor 0.800000 ccut 0.150000
```

```
  parameter setup save maxconf 1
  final glidescore
  report setup by glidescore nreport 500 -
   maxperlig 1 rmspose 0.500000 delpose 1.300000
  run
QUIT

CREATE
  build primary name lig type auto read maestro file -
"1ets_single_dock.mae" -
   tag LIG_ gotostruct 1
  build types name lig
QUIT

DOCK
  ligand name lig
  screen
  parameter save
  run
QUIT

DOCK
  smooth anneal 2
  ligand keep
  screen noscore refine maxref 100
  parameter save
  final glidescore read -
"1ets_single_grid.csc"
  minimize itmax 100 dielco 2.000000
 scoring ecvdw -25.000000 hbfilt -0.700000 metalfilt 0.000000 -
 hbpenal 3.000000
  report collect -
   rmspose 0.500000 delpose 1.300000
  run
QUIT

DOCK
  parameter clean final
  report -
   rmspose 0.500000 delpose 1.300000 write filename -
"1ets_single_dock"
  run
QUIT
```

```
END
```

The first `DOCK` task above (sometimes called the *setup* task) is somewhat similar to the one in the previous example, except that it reads rather than writes files, and that it indicates (through the `ligand` subtask) that one or more ligand structures are to be docked in this job.

`receptor`

The `readf` keyword indicates reading energy grids from files with the base name given, which in this case are the ones written in the previous example. `rdiel` means use the Coulomb potential computed with the r-dielectric (and stored in '`1ets_single_grid_coul2.fld`') for all energy calculations. Since everything is read from files, no other information about the receptor (active site, box size, etc.) is needed here.

`ligand` In subsequent `DOCK` tasks in this job, this subtask gives information about the ligand(s) to be docked. In this "setup" task, however, it simply indicates that there will be ligands, so that Glide can set up arrays to hold them. Even though there is only one ligand in this case, the `multiple` keyword must precede `maxat` and `maxrot`, which give the maximum number of atoms and rotatable bonds allowed in any ligand molecule in the current job. If we were indeed looping over multiple ligands, any one that exceeded these limits would be skipped. In addition, `maxat` is used in allocating storage for the ligand atom coordinates. The `ligvdwscale` keyword invokes scaling of the ligand vdW radii used in energy calculations, similar to `protvdwscale` above. As for the protein, omitting this keyword results in setting `factor 1.0` (no scaling), but we recommend using a scale factor < 1.0, and the Maestro interface writes `factor 0.8`, as shown. Again, see the FirstDiscovery Technical Notes for further discussion.

`parameter`

The `setup` keyword indicates that no actual calculations are to be done in this invocation of the task. Instead, the receptor and ligand data are simply read in and stored in dynamically allocated arrays. (The sizes of most of these arrays are read from the same grid files that contain their contents.) The `save` keyword indicates that these arrays should be retained in memory for use by subsequent invocations of the task. The `maxconf` keyword gives the dimension of dynamically allocated arrays that, in general, store information for multiple ligands or (externally generated) conformations. In this case, `maxconf 1` indicates a single ligand structure.

`screen` As with `readf` above, `readscreen` and `readgreed` here mean read the rough-score grids from the indicated files, and we don't need a `box` specification because it's in the same files. The following additional parameters give details of the rough-score screening task to follow.

- `maxkeep` Indicates the maximum number of ligand poses to be passed to the energy minimization. The number actually kept may be less than this, because fewer poses pass the various rough-score filters.
- `scorecut` Rough-score window for passing poses to grid-energy optimization. A pose survives if its rough-score is within `scorecut` of the best pose accumulated so far.

`report` Gives instructions for the "reporting" (output) of docked ligand *poses* (A pose is the structure of a single conformation of a single ligand, in a single position and orientation relative to the receptor). The setup task requires some information about what is to be reported and how.

- `setup` Indicates that we're specifying the reporting function here. Of course we can't actually collect data for the report (much less write it to output files) until we've actually docked the ligands. But we need to allocate space for the report data, etc.
- `by glidescore` Indicates that the poses to be reported will be sorted in order of the GlideScore scoring function.
- `nreport` The maximum number of poses to report. (The actual number may be smaller because fewer pass all screening or scoring tests, or because of the `maxperlig` keyword.
- `maxperlig` The maximum number of poses to report for any given ligand molecule. `maxperlig 1` is particularly useful for rapid screening of large databases, producing one pose for each of the `nreport` best-scoring ligands, which can then be subjected to more detailed calculations.
- `rmspose`
  `delpose` The rough-score and energy-optimization stages of a Glide may generate poses for a given ligand that

are similar to each other. In order to avoid duplication in the report, these keyword-value pairs indicate that two poses of the same ligand are to be considered distinct (and thus both reported if they otherwise qualify) only if the RMS deviation of their atomic positions exceeds the `rmspose` value, or the maximum deviation for any atom exceeds `delpose`. These keyword-value pairs must appear in *every* occurence of the `report` subtask in a given Glide input file.

The second `DOCK` task above runs the rough-score screening (except for pose refinement). Glide knows that it should do this (rather than just allocate arrays) because there is no `setup` keyword in the `parameter` subtask.

`ligand name lig`
: Copy the indicated Impact species into the Glide ligand arrays.

`screen`
: Run the rough-score screening using the parameters and information specified in the previous `DOCK` task.

The third `DOCK` task runs pose refinement and grid-energy optimization.

`smooth anneal 2`
: Needed here to tell Glide to use both the smoothed and "hard" potential energy surfaces in the actual minimization. It's possible to use `smooth anneal 2` in the first task in order to calculate or read both surfaces, but `smooth anneal 1` here to use only the smoothed one, or leave out the `smooth` subtask here to use only the hard surface.

`ligand keep`
: Continue to run calculations on the ligand structure used in the previous `DOCK` task, rather than reading in a new one.

`screen`

  `noscore`
  : Don't do the whole rough-score process here, because we did it in a previous task.

  `refine`
  : Use pose refinement.

  `maxref`
  : Maximum number of poses to keep after pose refinement.

`minimize`
: Minimize the Coulomb+vdW interaction energy (interpolated on the grids) for each ligand pose that survives through the rough-score and refinement steps.

`itmax` Maximum number of conjugate-gradient iterations

`dielco` Dielectric coefficient. If `cdiel` appears in the `receptor` subtask above, this is the dielectric constant. If `rdiel`, the dielectric is this number multiplied by the interatomic distance in Angstroms.

`scoring` Various filters for keeping poses after energy minimization.

`ecvdw` Reject any pose whose minimized Coul+vdW energy is greater (in this case, less negative) than this number.

`hbfilt` Reject any pose for which the hydrogen-bond contribution to GlideScore is greater than this number.

`metalfilt` Reject any pose for which the metal-binding contribution to GlideScore is greater than this number

`hbpenal` Assign this penalty in GlideScore for each buried polar interaction.

`report collect`
After minimization, and in this case GlideScore evaluation, collect data on top poses for final output. For a single ligand, this could be combined with the `report write` subtask in the next task. But for a loop over multiple ligands, collection is done inside the loop for each ligand, and final output is done once at the end of the job, outside the loop.

The fourth `DOCK` task writes the final output.

`parameter clean final`
Delete dynamically allocated arrays at the end of the task. The `final` keyword insures that the Glide report function is executed even if the last ligand's structure was problematic.

`report ... write filename ...`
Write the best poses (up to `nreport` of them, but subject to `maxperlig` and survival through all scoring filters) to the output files. For `filename` *base*, write the receptor structure and the ligand pose structures to *base*_pv.mae, and a summary of the poses and their scores to *base*.rept. The user can view the poses on screen, in conjunction with the receptor, by using the `Glide Pose Viewer`, available from the Maestro "Analysis" menu.

3.6.4 Example 3: Multiple Ligands, Flexible Docking

The above example treats a single conformation of a single ligand, to find the most favorable pose for docking to the given receptor. Probably the more common use of Glide is to determine which of a number of conformations, or which ligand of a number of candidates, has the most favorable interaction with the receptor. The `DOCK` task can be invoked repeatedly to handle multiple input ligand structures, as in the loop shown below using the DICE scripting language. (See Chapter 5 [Advanced Input Scripts], page 185 for details of DICE.) We recommend using a loop as shown here, over multiple ligands in a single file (Maestro or MDL SD format), with each structure a different ligand, and using Impact's internal conformation generator (subtask `confgen`) and torsional flexibility during grid-energy optimization (`flex` keyword in `minimize` subtask) to sample the conformational space of each ligand in turn.

After the example, we describe the ways in which this example differs from the single-structure example above.

```
write file "1ets_example_mult.out" -
      title "1ets_example_mult" *

PUT 0 INTO 'buildcheck'
PUT 1 INTO 'startlig'
PUT 0 INTO 'endlig'
PUT -1 INTO 'strucseq'



DOCK
  smooth anneal 2
  ligand multiple maxat 100 maxrot 15 -
   ligvdwscale factor 1.000000 ccut 0.150000
  receptor rdiel readf -
"1ets_single_grid"
  screen readscreen -
"1ets_single_grid.save" -
   greedy readgreed -
"1ets_single_grid_greedy.save" -
   maxkeep 5000 scorecut 100.000000
  parameter setup save maxconf 1000
  final glidescore
  report setup by glidescore nreport 500 -
   external file -
"1ets_example_mult.ext" -
   maxperlig 1 rmspose 0.500000 delpose 1.300000
```

```
  run
QUIT

CREATE
  build primary name lig type auto -
   read sd file -
"many.mol" -
   gotostruct 1
  build types name lig
QUIT

DOCK
  ligand reference name lig
  screen noscore
  parameter save
  run
QUIT

PUT 'startlig' INTO 'strucseq'
CREATE
  build primary check name lig type auto -
   read sd file -
"many.mol" -
   gotostruct 'startlig'

  build types name lig
QUIT
IF 'buildcheck' LT 0
  IF 'buildcheck' EQ -1
    PUT -
$"END OF LIGAND FILE:"$ -
INTO 'outmsg'
  ENDIF
  IF 'buildcheck' EQ -2
     PUT -
$"ERROR READING LIGAND FILE:"$ -
INTO 'outmsg'
  ENDIF
  SHOW 'outmsg'
PUT -
$"many.mol"$ -
INTO 'filemsg'
SHOW 'filemsg'
```

```
    PUT $"No ligands read; aborting."$ INTO 'outmsg'
    SHOW 'outmsg'
    GOTO ABORT
ENDIF

PUT 'startlig' INTO 'i'
WHILE ('endlig' LT 1 OR 'i' LE 'endlig')

DOCK
  ligand name lig
  screen
  parameter save
  confgen name lig -
   ecut 12.000000
  run
QUIT

DOCK
  smooth anneal 2
  ligand keep
  screen noscore refine maxref 400
  parameter save
  final glidescore read -
"1ets_single_grid.csc"
  minimize flex itmax 100 dielco 2.000000
 scoring ecvdw -25.000000 hbfilt -0.700000 metalfilt 0.000000 -
 hbpenal 3.000000
  report collect -
   rmspose 0.500000 delpose 1.300000
  run
QUIT

PUT 'i' + 1 INTO 'strucseq'
CREATE
  build primary check name lig type auto -
   read sd file -
"many.mol" -
   nextstruct
  build types name lig
QUIT

IF 'buildcheck' LT 0
  IF 'buildcheck' EQ -1
```

```
    PUT -
$"END OF LIGAND FILE:"$ -
INTO 'outmsg'
  ENDIF
  IF 'buildcheck' EQ -2
     PUT -
$"ERROR READING LIGAND FILE:"$ -
INTO 'outmsg'
  ENDIF
  SHOW 'outmsg'
PUT -
$"many.mol"$ -
INTO 'filemsg'
SHOW 'filemsg'
  PUT $"Proceeding with final processing of ligands."$ INTO 'outmsg'
  SHOW 'outmsg'
  GOTO BREAK
ENDIF

PUT 'i' + 1 INTO 'i'
ENDWHILE
:BREAK

DOCK
  parameter clean final
  report -
   rmspose 0.500000 delpose 1.300000 write filename -
"1ets_example_mult"
  run
QUIT
:ABORT

END
```

The first thing to notice about this example is the initialization of four DICE variables near the top. Of these, `'buildcheck'` is set in the Impact code (as a result of the `build primary check` command), and `'strucseq'` is read by Glide to determine a sequential ligand number that it both uses in its internal bookkeeping and writes to output files. `NOTE:` the `'strucseq'` variable *must* be present, and incremented as in `PUT 'i' + 1 INTO 'strucseq'` above, in any Glide job that docks ligands from more than one input structure, or if a reference ligand (see below) is present. Its omission in such cases will cause the entire job to fail. `'startlig'` and `'endlig'` are set and used only within the input file itself, to control the loop over ligands. In particu-

lar, `PUT 0 INTO 'endlig'`, combined with the subsequent `WHILE` command, means loop until the end of the ligand structure file. By using different settings for these variables, it is possible to run Glide for different segments of a large multi-ligand database at different times (or at the same time on different machines), without physically splitting up the file containing the ligand structures. The script `para_glide`, in the `$SCHRODINGER/utilities` directory, is useful for running such "parallel" Glide jobs.

The first (setup) `DOCK` task is almost identical to that in the previous, single-ligand case. The order of the subtasks (`ligand` before `receptor` here, the opposite order above) is irrelevant, both because the two subtasks are independent and because neither actually results in any action until the `run` subtask. The larger values of `maxconf` and `maxkeep` in this case are the ones we recommend for multiple ligands with internal conformation generation.

Another difference in this task is the presence of the `external file` specification in the `report setup` subtask. This indicates a file to which Glide writes poses that pass all tests, in the order they are generated. Glide writes its final output (see `report write` below) after processing this file to find and sort the best `nreport` poses in the order requested. The `glide_sort` script, in the `$SCHRODINGER/utilities` directory, is also available for post-processing of this file according to different (user-selectable) criteria, and sorting in order of different scoring functions, including customizable combinations of various terms in GlideScore. Writing poses to an external file also serves as a *checkpointing* facility. If a job is interrupted in the middle, the data remain available in the external file for all ligands already docked. Note that The `external file` sorting mechanism is not compatible with "rigid docking" jobs such as the example in the previous section,[2], or with "Score in place" jobs (see below). For rigid docking jobs (or `confgen` jobs if the `external file` specification is omitted), the poses that pass are stored and sorted in program memory instead. For "Score in place," only the single input pose is treated, so saving, sorting, and structural reporting are not relevant.

This example also differs from the previous one by the presence of a *reference ligand*. This is useful in cases where one of the ligands to be docked is a known binder to the receptor, with a co-crystallized structure available. That is not actually the case here, but we specify a reference ligand anyway, just to illustrate the syntax. `ligand reference name lig` indicates that the structure just read into species `lig` is the reference structure: if the first ligand actually docked is the same molecule as this structure (as determined by `build primary check` below), the output will include RMS deviations of its docked pose(s) from this reference structure. `screen noscore` indicates that no actual docking calculations are to be done on this reference struc-

[2] Actually, `external file` would work with that specific example, because there is only one input ligand structure. But it doesn't work in general.

ture in this task; just its input coordinates are stored for subsequent RMS comparisons.

Like the first one, the subsequent `DOCK` tasks here are also very similar to those in the previous example. The differences are the increase in `maxref` to the number recommended for a multiple-ligand job; the presence of the `confgen` subtask in the rough-scoring task, which invokes `FirstDiscovery`'s internal conformation generator; and the keyword `flex` in the `minimize` subtask, which enables ligand torsional flexibility during the grid-energy minimization. The execution of the task is changed by `confgen`, however, in that for each ligand structure read in, Glide loops over the conformations it generates. The specifications appearing in this `confgen` subtask have the following meanings:

`name lig` Generate conformations for the indicated species.

`ecut` Reject any conformation whose internal energy (torsional and 1-4 vdW terms only) is more than the specified amount (in kcal/mol) higher than that of the best (lowest-energy) conformation generated.

Other than the implicit loops over conformations generated by `confgen`, the main differences in the Glide procedure between this example and the previous one come from the nature of the input (ligand) structure file and the `CREATE` tasks that read it, and more important, from the DICE loop itself, and other control structures.

`build primary check`

Before storing the structure (and other actions normally invoked by `build primary` in a `CREATE` task), check whether it is the same molecule as the one previously read. For this purpose, two structures are considered to be the same molecule if they contain the same atom types (to the extent that atom type is encoded in the file), with the same connectivity, listed in the same order. If they do, Impact does not need to repeat the atomtyping procedure, or to reset other parameters. (Note: if there were no reference ligand, this would be the first structure read into the ligand species, so `build primary check` and the subsequent parsing of `'buildcheck'` would not be needed here. They would still be needed inside the loop, as described below.)

The result of `build primary check` is encoded in the value of the DICE variable `'buildcheck'`. The possible values are:

`1` Structures are the same molecule

`2` Structures are different molecules

`-1` End of file (no "next structure" to read)

`-2` Error reading next structure

`IF 'buildcheck' LT 0`
: If we hit end of file or error on reading the first ligand to be docked, we must exit the program.

  The `PUT` and `SHOW` commands here are simply to provide informative output. Note that `SHOW` writes only to the "main output" file (`1ets_example_mult.out` as specified in the `write file` command at the top), not to Standard Output (or the `.log` file to which it is redirected).

`GOTO ABORT`
: Jump to the label `:ABORT`, which is at the end of the command file.

`gotostruct 'startlig'`
: As noted above, `many.mol` is a multi-structure file in MDL's SD format. (Analogous syntax, with `read maestro file`, would be used to read such a file in Schrödinger's Maestro format.)[3] The keyword-value pair `gotostruct` *n* calls for reading from the *n*th structure in the file, where in this case *n* is the value of the DICE variable `'startlig'`, which we set to 1 at the top of this input file. Thus if we wanted to start at ligand 3001, the command at the top would be `PUT 3001 INTO 'startlig`.

`PUT 'startlig' INTO 'i'`
: Initialize the loop index.

`WHILE ('endlig' LT 1 OR 'i' LE 'endlig')`
: The loop control. If `'endlig'` is less than 1 (as it is set at the top), this is nominally an infinite loop. Fortunately, DICE provides a way of breaking out of such a loop, which we will do in case of end of file or unrecoverable error (see `GOTO BREAK` below). If `'endlig'` were 1 or greater, it would set a limit on the number of times through the loop (and thus the number of ligand structures to process), even if that meant exiting before end of file. Thus to run only through ligand 1000 (if there are that many), change the command at the top to `PUT 1000 INTO 'endlig'`.

`nextstruct`
: Read the next structure in the file.

[3] For PDB format, Glide reads single-structure files, one per ligand (or input conformation, if `confgen` is not used). In this case, the Impact input file would have to include commands for storing the names of these files in a list, and the `CREATE` task in the loop would read the file whose name is the element of this list given by the loop index.

`IF 'buildcheck' LT 0`
: This is the crucial control structure. We need to break out of the loop if we have encountered the end of the file or an error. The `PUT` and `SHOW` commands are as above (except for details of the messages), but the target of the `GOTO` is not.

`GOTO BREAK`
: Jump to the label `:BREAK`, which is outside the loop.

`PUT 'i' + 1 INTO 'i'`
: Increment the loop index.

`ENDWHILE` End of the loop.

The final output of this job consists of the structure file `1ets_example_mult_pv.mae`, and the report file `1ets_example_mult.rept`, which follows. In the actual files on disk, all the columns are one one long row, to enable you to load them into a spreadsheet. They are printed here in separate sections for space reasons.

```
REPORT OF BEST 5 POSES

 The receptor and sorted ligand structures written to the file
 1ets_example_mult_pv.mae  for use in the Pose Viewer

Rank    Title     Lig# Conf# Pose# Score GScore E(Cvdw) Eintern Emodel
==== ============ ==== ===== ===== ===== ====== ======= ======= ======
   1 Lorazepam       5     2   112 -6.47  -6.47   -31.9     0.6  -45.3
   2 indomethacin    4     4    84 -6.24  -6.24   -35.0     8.5  -47.2
   3 Atropine        1     3    16 -5.42  -5.42   -38.8     2.1  -57.1
   4 Ibuprofen       3    24   151 -5.37  -5.37   -27.3     1.8  -42.2
   5 Diflucan        2   340    24 -3.61  -3.61   -34.4     4.9  -42.3

                  Ehbond Emetal Eclash E(Coul) E(vdW)  RMSD
                  ====== ====== ====== ======= ====== ======
                    -1.9    0.0    0.0   -2.5   -29.3   --
                    -1.9    0.0    0.0   -6.5   -28.5   --
                    -1.4    0.0    0.0   -9.6   -29.1 61.597
                    -1.5    0.0    0.0   -4.9   -22.4   --
                    -1.1    0.0    0.0   -5.3   -29.1   --
```

```
GlideScore (GScore) is the sum of a constant = -1.0, plus other
contributions including the following:

   EHbond:  Hydrogen-bonding term
   Emetal:  Metal-binding term
   Eclash:  Penalty for steric clashes

(GScore = 10000.0 indicates that a given ligand pose failed one
or more criteria for computing GScore.  Depending on which ones
it failed, the components of GScore may not be valid either.)

ECvdW is the non-bonded interaction energy (Coulomb plus
van der Waals) between the ligand and the receptor.
Emodel is a specific combination of GScore, ECvdW, and Eint,
which is the internal torsional energy of the ligand conformer.
```

As requested with `maxperlig 1`, this file contains information on one structure per ligand. For comparison of different ligands, the structures are sorted in order of increasing GlideScore (`GScore`), with the "best" ligand at the top. In choosing the best pose (or the best `maxperlig` poses) within the set of final structures for a single ligand, however, Glide uses the `Emodel` score rather than GlideScore. `Emodel` is a weighted average of the GlideScore function and the Coulomb+vdW interaction energy (ECvdW) for a given pose, and is better suited than GlideScore for comparing poses of a single ligand.

For each pose, the report file lists its rank in GlideScore order, the ligand "title" taken from the input structure file, and the ligand number in the order the ligands were read in. (This includes any skipped ligands. For instance, if ligand #5, Lorazepam, were not processed for some reason, but processing of other ligands continued after it, then progesterone would still be listed as ligand #6.) It also gives conformation and pose numbers according to Glide's internal ordering, which are useful for distinguishing different structures of the same ligand (when `maxperlig >` 1). The subsequent columns include GlideScore, Emodel, various components of these, and if a reference structure was specified and the first ligand (in the order they were read in) is the same molecule as the reference, the heavy-atom RMS deviation (in Angstroms) of poses of that ligand from the reference structure. (The RMSD here includes the effects of translation and rigid rotation of the ligand, not just conformational differences. The high RMSD value in this case occurs because the reference ligand in this case was the input structure of the first docked ligand, which in fact is not a cocrystallized ligand for this receptor.) For other molecules (or if there was no reference structure), `--` appears in the RMSD column. The "Score" column in the above table is the same as GlideScore because by default, Glide ranks poses according to this scoring function. By specifying `by energy` in the `report setup` command, or by using the `glide_sort` post-processing script with appropriate flags, the

user may choose to sort on some other score such as ECvdW (`by energy`), or some custom combination of various terms in the table (`glide_sort`). The "Score" column will always contain the value of the function by which the poses are ranked. If the keyword-value pair `verbosity 2` (or greater) appears in a `parameter` subtask before (or in the same `DOCK` task as) the `report write` command, the report file shows the ligand center coordinates and Euler angles of each pose, instead of some of the score components.

GlideScore values of 10000.0 indicate that GlideScore was in fact not calculated for a given pose. This occurs when the pose fails one (or more) of the criteria specified in the `scoring` subtask.

3.6.5 Example 4: Scoring in Place

In addition to searching for the best conformation and pose of one or more ligands, Glide can also evaluate its scoring functions on an input structure. To request this *scoring in place* feature, use the keyword `singlep` (for "single-point" energy or scoring) in the `ligand` subtask of a `DOCK` task after the setup. If this appears in a loop, scoring in place will be done for each input structure read in the loop. Note in the following input file that the `DOCK` tasks for rough-score screening and energy minimization are combined into one; but no screening or minimization actually takes place. As noted above, the `external file` keywords cannot be used in the `report setup` subtask for such a job. Glide does not currently report an error if they are used (because they may occur in a separate `DOCK` task from the `singlep` keyword), but the job will not run correctly if they are present.

```
write file "1ets_single_inplace.out" -
      title "1ets_single_inplace" *

PUT 0 INTO 'buildcheck'
PUT 1 INTO 'startlig'
PUT 0 INTO 'endlig'
PUT -1 INTO 'strucseq'

DOCK
  smooth anneal 2
  ligand multiple maxat 100 maxrot 15 -
   ligvdwscale factor 1.000000 ccut 0.150000
  receptor rdiel readf -
"1ets_single_grid"
  screen readscreen -
"1ets_single_grid.save" -
   greedy readgreed -
"1ets_single_grid_greedy.save" -
   maxkeep 1000 scorecut 100.000000
```

```
  parameter setup save maxconf 1
  final glidescore
  report setup by glidescore nreport 500 -
   maxperlig 1 rmspose 0.500000 delpose 1.300000
  run
QUIT

PUT 0 INTO 'strucseq'
CREATE
  build primary name lig type auto read maestro file -
"1ets_single_inplace.mae" -
   tag LIG_ gotostruct 1
  build types name lig
QUIT

DOCK
  smooth anneal 2
  ligand name lig singlep
  screen noscore refine maxref 100
  parameter save
  final glidescore read -
"1ets_single_grid.csc"
  minimize itmax 100 dielco 2.000000
 scoring ecvdw -25.000000 hbfilt -0.700000 metalfilt 0.000000 -
 hbpenal 3.000000
  report collect -
   rmspose 0.500000 delpose 1.300000
  run
QUIT

DOCK
  parameter clean final
  report -
   rmspose 0.500000 delpose 1.300000 write filename -
"1ets_single_inplace"
  run
QUIT

END
```

The output of a score-in-place job is written to a `.scor` file, in this case `1ets_single_inplace.scor`. This file gives the components of GlideScore and ECvdW for each input ligand (in this case only one). There is no

structural output file (like the `_pv.mae` files in previous examples), because the structure is the same as in the input file.

```
-------------------------------------------------------------------------------
Lig # Title GScore  HBond Metal  Lipo  RotB Clash BuryP   ECvdW  ECoul   EvdW
    1       -11.40  -4.55  0.00 -6.58  0.73  0.00  0.00  -70.01 -19.98 -50.03
-------------------------------------------------------------------------------


 GlideScore (GScore) is the sum of a constant = -1.0, plus the
 following contributions:

    HBond:  Hydrogen-bonding term
    Metal:  Metal-binding term
    Lipo:   Lipophilic contact term
    RotB:   Penalty for freezing rotatable bonds
    Clash:  Penalty for steric clashes
    BuryP:  Penalty for buried polar groups

 (GScore = 10000.0 indicates that a given ligand pose failed one
 or more criteria for computing GScore.  Depending on which ones
 it failed, the components of GScore may not be valid either.)

 ECvdW is the non-bonded interaction energy (Coulomb plus
 van der Waals) between the ligand and the receptor.
```

3.6.6 Example 5: Glide Constraints

Glide constraints are requirements that docked ligands have specific interactions with the receptor. During grid generation, you can specify up to ten "constraint atoms" in the receptor, to which all ligand poses must make either hydrogen bonds or metal-binding interactions (for metal ions in the receptor only) in order to be considered for docking. If you specify a constraint atom that is part of a functional group, and has a structural symmetry with one or more other atoms of the same chemical type in the group, then Glide will automatically include the symmetry-related atoms as part of the same constraint specification, and will consider a ligand interaction with any one of them as satisfying the constraint. The ligand atom types that can satisfy metal-binding constraints are the same as those that can be hydrogen bond acceptors. In addition, for metal-binding only, you may require that ligand atoms be in a specified formal charge state in order to be considered as satisfying the constraint: "Must be charged" (the default, and usually the best choice), "Must be neutral," or "May be either charged or neutral." Whichever you choose, Glide will apply that requirement for binding to all receptor metal ions you have selected for constraints.

Because Glide incorporates any constraint specifications in several of its hierarchical filters (and incurs little additional computational cost in doing so), using constraints can achieve significant acceleration of docking calculations. This occurs both because large regions of pose space can be quickly eliminated (as well as entire ligands that don't have the right kind of atoms to satisfy the constraints), and because the number of poses that need to be saved in order to find the desired ones is substantially reduced. In particular, the recommended values of the `maxkeep` and `maxref` parameters with constraints are 500 and 40, each 1/10 of the recommended value without constraints. In tests at Schrödinger, we have accelerated docking calculations by a factor of about 2.5. In addition, by eliminating "false positive" ligands or poses, constraints can improve enrichment factors in database screening. And by restricting the allowed binding modes, judiciously chosen constraints may also improve docking accuracy.

As the following two examples demonstrate, you must specify constraints in the `receptor` subtask of the initial `DOCK` task, in both the grid generation and ligand docking jobs. The grid generation job needs to know which receptor atoms you want to require ligand atoms to interact with. It extracts or calculates information about these atoms (such as their types and locations) that the docking job will use in enforcing the constraints, and writes the information to a file. The docking job needs to know that it must read this file and enforce the constraints it describes. The default name for this file is *base*.cons, where *base* is the "base name" specified with the `readf` and `writef` keywords.

```
CREATE
  build primary name recep type auto -
    read maestro file -
"1dm2_ref.mae" -
    tag REC_
  build types name recep
QUIT

DOCK
  smooth anneal 2
  receptor name recep -
   constraints ncons 3 consatom 603 consatom 623 consatom 2881 -
   writef -
"1dm2_conssite" -
   protvdwscale factor 1.000000 ccut 0.250000 -
   box center read xcent 103.193108 ycent 99.510063 zcent 81.719223 -
   boxxrange 32.000000 boxyrange 32.000000 boxzrange 32.000000 -
   actxrange 32.000000 actyrange 32.000000 actzrange 32.000000
  screen greedy -
   box center read xcent 103.193108 ycent 99.510063 zcent 81.719223 -
```

```
   ligxrange 12.000000 ligyrange 12.000000 ligzrange 12.000000 -
   writescreen -
"1dm2_conssite.save" -
   writegreed -
"1dm2_conssite_greedy.save" -
   maxkeep 5000 scorecut 100.000000
  parameter clean
  final glidescore
  report setup by glidescore nreport 500 -
   maxperlig 1 rmspose 0.000000 delpose 0.000000
  run
QUIT

END
```

In this job, we specify three constraint atoms (`ncons 3`) in the protein CDK-2. We list each (`consatom`) by its atom index in the input structure file `1dm2_ref.mae`, derived from Protein Data Bank entry 1DM2. These three atoms are the backbone oxygens in residues `GLU 81` and `LEU 83`, and the backbone (amide) hydrogen in `LEU 83`, which are "lined up" in close proximity in the crystal structure. The cocrystallized ligand, hymenialddisene, makes hydrogen bonds to all three.

In a ligand docking job, you may specify up to four of the constraints defined in the previous gridgen job, for Glide to enforce when docking ligands. You specify the number of constraints to be applied with the `nusecons` keyword, followed by that number of `nusecons` *num* keyword-value pairs, where each *num* is the index of a constraint in the order they were specified in the grid generation job. Thus in the following input file excerpts, `nusecons 2 usecons 1 usecons 3` tells Glide to require ligands to interact with the `GLU 81` oxygen and the `LEU 83` hydrogen, the first and third constraint atoms specified in the gridgen job shown above, but not with the `LEU 83` oxygen. If you request constraints in a docking job but omit the `nusecons` and `usecons` keywords, Glide will enforce all the constraints specified in the gridgen job, or the first four if there were more than four specified. This is the same behavior as in previous versions of Glide, where you could specify only up to four constraints in the gridgen job, and any docking job using those grids that requested constraints would enforce all of them. Note that in order to enable selection of a proper subset of constraints for docking, the constraint information file that the gridgen job writes now has additional information, so files written by Glide versions prior to 3.0 may not be compatible with docking jobs in version 3.0 and later.

In the excerpts shown below from a ligand docking job, the first `receptor` subtask indicates that we want to apply constraints set up in a prior grid generation job. In this case, everything except the word `constraints` itself, and the `nusecons` and `usecons` specifications described above, is actually

unnecessary because we are using default values, but we include the other specifications here for purposes of illustration. For instance, the keyword-value pair `consname "1dm2_conssite.cons"` gives the name of the file containing receptor constraints information. In this case, the name is the same as what would have been built by default from the base name appearing in `readf "1dm2_conssite"` to specify other grid files. But we could instead have specified a different constraint file name, but still used the `"1dm2_conssite"` files for energy grids.

The keywords `restcoef` and `restexp` give parameters of a *restraining potential* that Glide uses to enforce the constraints during grid-energy optimization. This potential is a Gaussian function of the distance r between a polar hydrogen and a hydrogen-bond acceptor, or a metal ion and its coordinating atom in the ligand, centered at the equilibrium distance for the given interaction:

$$V(r) = -A \exp\left[-b\,(r - r_0)^2\right]$$

where r_0 is the equilibrium distance, $1.85\mathring{A}$ for a hydrogen bond or $2.11\mathring{A}$ for a metal-ligand interaction. The default values for the coefficients A and b are those shown below for `restcoef` and `restexp`: $A = 30.0 kcal/mol$ and $b = 0.3\mathring{A}^{-2}$. These values of the parameters have yielded good results in our simulations, but we do not claim that they are the only reasonable values.

```
DOCK
...
  receptor rdiel readf -
"1dm2_conssite" -
  constraints consname "1dm2_conssite.cons" -
  nusecons 2 usecons 1 usecons 3 -
  restcoef 30.0 restexp 0.3
  screen readscreen -
"1dm2_conssite.save" -
   greedy readgreed -
"1dm2_conssite_greedy.save" -
   maxkeep 500 scorecut 100.000000
...
QUIT
DOCK
  smooth anneal 2
  ligand keep
  screen noscore refine maxref 40
  parameter save
  final glidescore read -
"1dm2_conssite.csc"
```

```
 minimize flex itmax 100 dielco 2.000000
scoring ecvdw 0.000000 hbfilt 0.00000 metalfilt 0.000000 -
hbpenal 3.000000 hbwidth 0.000000
 report collect -
  rmspose 0.500000 delpose 1.300000
 run
QUIT
```

The first `DOCK` task above also shows the parameter value `maxkeep 500`, and the second shows `maxref 40`. As noted, these settings are 1/10 of the recommended values without constraints, and contribute significantly to the speedup in execution time. We have achieved good results with these values, but it is possible that higher values (and thus less speedup) may be necessary, or lower ones (and more speedup) sufficient, for keeping the desired poses in different systems.

3.6.7 Subtask Smooth

Request smoothing of energy functions used in constructing grids.

- `smooth [cwall` *val*`] [csoft` *val*`] [vsoft` *val*`] [anneal [1|2]]`

`cwall, csoft`
: Smoothing parameters for Coulomb energy.

`vsoft`
: Smoothing parameter for Lennard-Jones energy.

`anneal`
: Controls minimization on smoothed and/or unsmoothed energy surface.

Both smoothing functions work by evaluating the standard energy functions for two atoms at an *effective distance* that is positive when the actual distance between the atoms is zero. For the Coulomb energy, the effective distance at an actual distance d is given by

```
ceff = sqrt[d * d + cwall * cwall * exp(  - (d * d) / csoft)],
```

and for the Lennard-Jones energy, by

```
veff = d + vwall * exp( - (d * d) / vsoft).
```

(Note that in each case, the *wall* parameter is the value of the effective radius at d = 0, and the *soft* parameter determines how rapidly the function reverts to its unsmoothed value as d increases, with a larger parameter giving a slower (or "softer") transition.)

Note that `vwall` is not user-specifiable. Instead, for the contribution of a given protein atom, Glide uses half of the Lennard-Jones σ parameter for that atom. The default values for the other parameters are `cwall` = 2.0 Å,

and `csoft` = `vsoft` = 4.0 Å^2. All of the parameters must be positive numbers; if the user specifies any negative, all are ignored, a warning is issued, and smoothing is not performed. In addition, if the softness parameters are below certain lower bounds, the resulting smoothed potential will have a local maximum (for a repulsive potential) at some positive distance, and a spurious minimum rather than a maximum at zero distance. For Coulomb smoothing, the lower bound is `csoft` = `cwall` * `cwall`. For Lennard-Jones, since `vwall` varies with the protein atom type, we use a lower bound large enough to accommodate the largest $\sigma/2$ in paramstd.dat (3.358 Å for the Cs^+ ion, which gives a lower bound of `vsoft` = 2.075 Å^2). If the user specifies a softness lower than the applicable lower bound, a warning is issued and the parameter is reset to equal the lower bound.

With the smoothing functions, Glide offers the option of *annealing* during grid-energy minimization. This involves starting the minimization on the potential-energy surface defined by the smoothed functions, and gradually shifting to the unsmoothed functions. The advantage of this procedure is to allow exploration of more regions of ligand pose and conformational space early in the process (because the smoothed functions have lower barriers), while still ending at a minimum of the original grid potential rather than at a pose whose energy is made artificially low by smoothing. Specifying `smooth anneal 2` when calculating grids will result in both smoothed and unsmoothed functions being calculated (and saved to disk); the same specification in the task where minimization is done will result in annealing during minimization. `Smooth anneal 1` means calculate, save, and/or minimize on only the smoothed surface. To calculate or minimize on only the unsmoothed potentials, omit the `smooth` subtask entirely. We strongly recommend using `smooth anneal 2` in all cases.

3.6.8 Subtask Receptor

Specify receptor molecule(s) and active site.

- `receptor [writef` *writebase*`] [readf` *readbase*`] -`
  `[cdiel | rdiel | nil] -`
  `[writecdie | writerdie | nil] -`
  `[name` *spec* `[mole [`*mol* `| all]] -`
  `[constraints [ncons` *num_cons* `-`
  `(consatom` *num*`)` repeated *num_cons* times`] -`
  `[consname` *file*`] [restcoef` *val*`][restexp` *val*`] -`
  `[metalbind [charged | neutral | any]] -`
  `[bsize` *size*`] [nlev` *nlevels*`] -`
  `[(scut` *val*`)` repeated *nlevels*-1 times`] -`
  `[box center read xcent` *val* `ycent` *val* `zcent` *val* `-`
  `boxxr` *val* `boxyr` *val* `boxzr` *val* `-`
  `actxr` *val* `actyr` *val* `actzr` *val*`] -`

`[active nsec` *num_sections* `-`
`(fres` *num* `lres` *num*`)` repeated *num_sections* times `-`
`[buffer` *val*`]] [readsurface` *file*`] [writesurface` *file*`]`

`writef`
`readf` Write/read energy grids (or *fields*) to/from disk files. `writef` writes adaptive grid structure information to *writebase*.grd, Coulomb potential (constant dielectric) to *writebase*_coul.fld, Coulomb potential (linear dielectric) to *writebase*_coul2.fld, and Lennard-Jones grids to *writebase*_vdw.fld. `readf` reads the files if they exist, and calculates the energy grids from scratch if they don't (and there is a receptor structure specified with the `name` keyword). At least one of `readf` and `writef` should always be specified. If both are specified, Impact reads whatever files are present, and calculates and writes those that aren't. (If *readbase* and *writebase* are different, Impact reads from the former and writes to the latter.) The files specified by `readf` should of course have previously been written as a result of a `writef` in a previous docking task.

`cdiel`
`rdiel` Specifies whether the Coulomb energy should be calculated assuming a constant dielectric (`cdiel`) or a dielectric linear in the interatomic distance (`rdiel`). If neither is specified, the default is to use the constant dielectric. If both `cdiel` and `rdiel` are specified, `rdiel` wins, i.e., the linear dielectric is used. We recommend `rdiel` (and `dielco` 2.0 in the `minimize` subtask), to account, however roughly, for solvent effects. Note that these keywords affect which grid file is read, not the original calculation and writing of the grids, which is controlled by `writecdie`/`writerdie`.

`writecdie`
`writerdie`
Specifies whether Coulomb grids are written to disk for the constant (`writecdie`) or linear distance-dependent (`writerdie`) dielectric model. If neither is specified, both grids are written. (If both are specified, the one that comes last wins.) Because grid files are large and we recommend always using the linear dielectric, we also recommend using `writerdie` to save disk space.

`name`
`mole` Specifies the Impact species that includes the receptor molecule(s). If the species contains more than one molecule (apart from bound solvent), then the `mole` keyword is *required*,

with either the name (*mol*) of a single molecule, or `all` to indicate all molecules in the species are included.

`constraints`
: Require ligand poses to make specified interactions with the receptor. As noted above (see Section 3.6.6 [Constraints (Docking)], page 125), the `constraints` keyword must appear in both grid generation and ligand docking jobs in order for constraints to be used. The appearance of the following keywords depends on the type of job.

  `ncons`
  `consatom`
  : These keywords appear in grid generation jobs. `Ncons` indicates how many independent receptor atoms (not related to each other by symmetry) the ligand is required to interact with, and the `consatom` specifications list these atoms by their indices in the input receptor structure file.

  `consname`
  : This may appear in either grid generation or ligand docking jobs. It specifies an alternative file name for writing or reading information about the receptor constraint atoms. The default is *writefbase*`.cons` or *readfbase*`.cons`, whichever is present in the same `receptor` subtask.

  `restcoef`
  `restexp`
  : These may be specified in a ligand docking job. They are the depth (multiplicative coefficient, without the negative sign) and inverse square half-width (coefficient of the exponent) in a Gaussian potential function added to enforce the constraints during energy minimization. For the form of the potential, See Section 3.6.6 [Constraints (Docking)], page 125.

  `metalbind`
  : This may appear in a ligand docking job. It specifies that any ligand atom that satisfies a constraint to bind a metal ion in the receptor must bear a nonzero formal charge (`charged`), must bear zero formal charge (`neutral`), or may be in any formal charge state (`any`). The default, and the recommended value, is `charged`.

`bsize`
: The size of the finest grid spacing for the energy grids, in Angstroms. Default 0.4.

`nlev` Number of *levels* of the adaptive grid. At each successive level (farther from the receptor surface), the grid spacing is twice what it is at the previous level. Thus if the smallest grid spacing is *size*, then the largest is $2^{(nlevels-1)} * size$. Default *nlevels* = 4.

`scut` Distances from the receptor (the closest receptor surface point) at which the grid spacing changes. Thus

```
bsize 0.4  nlev 2  scut 1.0
```

means that the grid spacing is 0.4 Å for points closer than 1.0 Å from the receptor surface, and 0.8 Å farther away. If there is more than one `scut` value (i.e., if *nlevels* > 2), they must be given in *descending* order. The default (corresponding to `bsize 0.4 nlev 4`) is `scut 4.4 scut 2.8 scut 2.0`.

`box` Explicitly specify the rectangular box in which the energy grid is defined, rather than building it based on a specification of active site residues.

`center read`
: Gives the three Cartesian coordinates of the center of the box, as the the numbers following `xcent`, `ycent`, and `zcent`. The keyword `read` is required here because another option is available with the `center` keyword in the `screen` subtask, and the same code is used to parse the `box` input in both subtasks.

`boxxr`
`boxyr`
`boxzr`
: The size of the grid box (in Angstroms) in the x, y, and z directions. That is, the x-coordinates of the grid points in the box range from approximately `xcent` − `boxxr`/2 to `xcent` + `boxxr`/2. This is approximate because extra space may be added to the ends of the box so that it contains a whole number of elementary cubes of the grid.

`actxr`
`actyr`
`actzr`
: Dimensions (Angstroms) of the box used to determine "active" residues whose surface is used in early rough-score filters. Surface points are calculated for all residues that have any atom in this box. In general this should be the same size as the grid box, but memory limitations in the surface-generation algorithm require a box no larger than 50 Å on a side.

`active` An alternative method of defining the dimensions of the grid and "active surface" boxes. Specifies which residues are to be considered the active site of the receptor. The grid box is computed using the largest and smallest x-, y-, and z-coordinates of atoms in these residues, and adding a distance in each direction (positive and negative) as specified with the `buffer` keyword. As when directly specifying `actxr`, etc., surface points are actually generated for all residues with any atom in the box, not just the ones specified here. The initial `active` residues are specified as *num_sections* ranges, each given by a `fres lres` pair. Each `fres` value must be greater than the previous `lres` (the first must be greater than zero), and each `lres` must be greater than or equal to the corresponding `fres` (with equality implying a range consisting of a single residue). The maximum value of *num_sections* is 100. (If you need more than that, consider filling in to combine several ranges into one.) If neither `active` nor `box` is present, then all residues of the receptor are considered to be in the active site, with a `buffer` of the default size, 11.0 Angstroms.

`nsec` Indicates that the active site residues are given by the following `fres` *num1* `lres` *num2* pairs, where each of the *num_sections* pairs indicates that all residues in the range *num1* through *num2*, inclusive, are part of the active site. (Note that such a "range" may consist of a single residue, as `fres 79 lres 79`.)

`buffer` Indicates that the box in which the grids are defined extends a distance *bufval* Angstroms beyond the minimal box that encloses the active site, in each of the positive and negative x, y, and z directions. Default is 11.0.

`readsurface`
`writesurface`
Read/write receptor surface points from/to the indicated file. The surface points are calculated from the positions and radii of receptor atoms in residues contained in the "active" box defined by either `actxr`, etc., or `active`, and are used in early filters in the rough-score screening step. The surface calculation is somewhat time-consuming, so it may be convenient to store the points for future use, particularly in runs where the energy grids are not being recalculated (which takes a much longer time) but the rough-score grids are (which is quite fast, so recalculating the surface can add significantly to it).

3.6.9 Subtask Ligand

Specify ligand molecule.

- `ligand keep`
- `ligand multiple maxat` *nat* `[maxrot` *nbond*`] -`
  `[amideoff]`
- `ligand name` *spec* `[mole` *mol*`] -`
  `[init [zero | rand [`*randopts*`] | read` *posespec*`] -`
  `[cminit [zero | box | lig | grid` *gridspec*`] -`
  `[reference] [noelec] [[stdrot | norot]] -`
  `[multiple maxat` *nat* `maxmol` *nmol*`] -`
  `[new]`

`keep` Indicates that no new parameters or coordinates are to be read in for the ligand, but that there is still a ligand present. The docking calculation will not run correctly if there is no `ligand` subtask present, so `ligand keep` is required in invocations of the `DOCK` task that do not introduce a new ligand conformation, as in a pose refinement and energy minimization step after a rough-score screening task (possibly in a loop over externally generated conformers) for the same ligand. If the `keep` keyword appears in a `ligand` subtask, all other keywords in that subtask are ignored.

`multiple` The keyword `multiple` is used here for historical reasons. It should really be called `ligand size`, because it is necessary even in single-ligand jobs that contain a "setup" `DOCK` task that doesn't dock (or otherwise specify) any specific ligand. For such a single-ligand job, `maxat` and `maxrot` should give the number of atoms and rotatable bonds in that ligand. For multiple-ligand jobs, they give bounds on the size of ligands that will be considered, that is, input ligands with more atoms or rotatable bonds will be skipped. The defaults are `maxat 300 maxrot 35`, and the maximum allowed value for `maxat` is 1000. The `amideoff` keyword indicates that amide bonds should not be considered rotatable. By default, they are rotatable. The `multiple` keyword must appear in the `ligand` subtask of the first `DOCK` task of an Impact input file.

`name` The name of the species in which the ligand molecule is to be found.

`mole` The name of the ligand molecule within species *spec*. Note that Glide can only handle single molecules (as defined in the `create` task) as ligands, so if *spec* contains more than one molecule, `mole` *mol* is *required*.

`reference`

Specifies that the current ligand molecule (the one most recently read in to the specified species) is to be taken as the reference conformation for root-mean-square deviation (rmsd) calculations. Such calculations are only meaningful, and Glide only does them, for ligands that are the same molecule as the reference. Glide also issues a warning that rmsd calculations may not be meaningful for a multiple-ligand job, but the rmsds it does calculate should be correct. In general (and in jobs set up and/or launched from the Maestro user interface), no actual docking calculations are done in the `DOCK` task that specifies the reference ligand. It is of course possible to include the reference ligand in a subsequent `DOCK` task that actually does dock it.

`init`
`cminit` Specify the initial pose of the ligand for energy minimization, if rough-score screening is not performed. The usual specification of these keywords (and the default) is `init zero cminit lig`. If rough-score screening is run, these keywords are ignored, because the initial poses for minimization are those that survive screening.

`init zero` Specifies that the ligand center should start at the origin of coordinates, unless displaced by `cminit`.

`init rand [cmrange` *val*`] [thetarange` *val*`] [phirange` *val*`] [psirange` *val*`] [seed` *num*`]`
Specifies a random starting pose. This is chosen in the ranges given with the keywords `cmrange`, `thetarange`, `phirange`, and `psirange`. That is, each Cartesian coordinate of the center position starts in the range (-`cmrange`/2) to (`cmrange`/2) Angstroms about the position specified by `cminit`; the Euler angle θ starts in the range 0 to (`thetarange`) degrees; ϕ starts in the range (-`phirange`/2) to (`phirange`/2), and similarly for ψ. `iseed` is a seed for the random number generator. The defaults are `cmrange 2.0 thetarange 30.0 phirange 60.0 psirange 60.0 iseed 137`.

`init read xcm` *val* `ycm` *val* `zcm` *val* `phi` *val* `theta` *val* `psi` *val*
Initializes the ligand to the specified pose (center coordinates in Ansgtroms, angles in degrees), again subject to modification by `cminit`.

`cminit zero`
: Specifies that the starting position of the ligand center should be at the origin, or unmodified from the position specified by `init`. Thus specifying `cminit zero` with `init zero` or `init rand` would indeed place the ligand at the origin of coordinates, or randomly in the specified range around it, which is unlikely to be useful. But `cminit zero` is the default with `init read`, in which case it leaves the ligand at the specified position.

`cminit lig`
: Starts the ligand at the position given in the input file. This is the default with `init zero` and `init rand`. In the latter case, the starting position is randomly displaced in the specified range about the input position.

`noelec`
: Turn off electrostatic interactions, by setting partial charges to zero for all atoms in the current ligand. This is reset for each ligand structure read in, so the `noelec` keyword must appear in the first `DOCK` subtask for each ligand, e.g. in the ligand loop. Note also that the final reported Coulomb energy for a ligand pose is a "scaled" energy that depends on formal charges as well as partial charges, and `noelec` does not zero the formal charges, so the output files (.rept and .mae) may report nonzero Coulomb energies even if `noelec` is set. But `noelec` does guarantee that no electrostatic interactions are included in the energy minimization and Monte Carlo steps, in which the final poses are produced.

`stdrot`
`norot`
: Control the starting orientation of the ligand. `stdrot` places the ligand in a standard orientation, with its *diameter* (the line segment connecting the two most widely separated ligand atoms) pointing along the z-axis. `norot` leaves the ligand in the orientation specified with the `init` keyword. With `init read ... cminit zero`, the ligand starts in the user-specified position and orientation, and the default is `norot` to leave it there. In all other cases, the default is `stdrot`. The Euler angles that define poses, in both phases of the docking calculation, are then defined relative to the standard orientation.

`new`
: Indicates that the current ligand molecule has a distinct structure (not just a different conformation) from the preceding one. This keyword is usually unnecessary, because the newness of the

ligand is perceived automatically by `build primary check` in its `CREATE` task.

3.6.10 Subtask Parameter

Specify various parameters and flags.

- `parameter [verbosity` *num*`] [maxconf` *num*`] -`
  `[setup] [save] [clean]`

This subtask sets certain controls on the overall operation of the task.

`verbosity`
: Controls the amount of information printed to STDOUT and to the main output file. The default is `verbosity 1`, which should be sufficient for most users' purposes. Certain things are printed independent of the value of this parameter, including the summary (labeled `DOCKING RESULTS`) of the best-scoring poses (by various criteria) for each ligand and their scores. `verbosity 0` (or less, which is equivalent to 0), prints a bare minimum of additional information. Values higher than 2 or 3, and especially higher than 5, print information that's very unlikely to be useful to anyone other than developers and debuggers, and can result in extremely large output files. A given `verbosity` level remains in effect unless and until the `parameter` subtask of a subsequent `DOCK` task changes it.

`maxconf`
: The maximum number of ligand conformations to be processed in this job. This parameter sets the size of a dynamically allocated array, and attempting to read conformations beyond this number will result in an error.

`setup`
: Indicates that the current invocation of the `DOCK` task is only for the purpose of setting up arrays (including rough-score and energy grids) for use by subsequent invocations in the same Impact job (as in multi-conformation loops). Though there will in general be a `screen` subtask along with `parameter setup` to set parameters for the rough-score screening, no actual screening calculation on the ligand will actually be done at this point. (Nor will minimization, which there's no reason to specify at all in a task with `parameter setup`.)

`save`
`clean`
: Specify the disposition of various dynamically allocated arrays (including those that hold the rough-score grids, and the ligand and receptor coordinates copied from the main Impact arrays) at the end of the current invocation of the `DOCK` task. `save` means leave them in place for use by subsequent invocations of

the task, `clean` means delete them, which means any subsequent invocations must build them again. If `setup` is specified, `save` is the default. (Indeed, `setup clean` doesn't make sense: set up the grids, don't use them, and then throw them away.) If neither `setup` nor `save` is specified, `clean` is the default. (But it doesn't hurt to specify `save` or `clean`, where appropriate, even if it is the default.)

3.6.11 Subtask Confgen

Request internal generation of ligand conformers.

- `confgen -`
  `ecut` *val* `[baddist` *val*`] -`
  `[maxcore` *num*`] [corescale` *val*`] -`
  `[noringconf]`

This is the recommended method of incorporating ligand flexibility into Glide, especially in a multi-ligand job. As shown in the examples above, the command sequence in an Impact input file should be different depending on whether there is one input structure per ligand, with `confgen` specified, or multiple structures assumed to be externally generated conformers for each ligand. In the latter case, we recommend a loop over `screen` subtasks, to run the first stages of rough-score screening (through greedy score evaluation) on all of the conformers of a given ligand, before running pose refinement, grid-energy optimization, and final (`GlideScore`) scoring on all poses that pass the first stages for that ligand. With `confgen`, by contrast, the loop over the internally generated conformations is specified by a single `screen` subtask, so the subsequent steps should ensue immediately.

By default, `confgen` generates alternative ring conformations for five and six membered non-aromatic rings. To turn off this procedure, use the `noringconf` keyword. For six membered rings, the alternative chair conformation is generated if the equatorial–axial conformational change of the substituents is empirically not too energetically costly. The five membered rings currently treated are sugar rings and five membered rings with N and/or S atoms. The alternative sugar ring conformation generated from the input consists of the energetically preferred pseudorotation. Five membered rings with N or S atoms have a second ring conformation generated by rotation of the out-of-plane corner.

`ecut` This parameter is the energy cutoff used in the gas phase conformation generation. Conformations with an energy above ecut relative to the lowest energy conformation are not considered. Note that the energy scale here is with respect to the model torsion/1-4 vdW confgen potential and not a full force field potential.

`baddist` The `baddist` parameter is used to generate a pair list for intra ligand repulsion terms used in the gas phase generation of conformations. We do not recommend changing this parameter from its default value of 2.45 Å.

`maxcore` The `maxcore` parameter allows the user to define a maximum number of core conformations to be generated. The default behavior is to use a functional form depending on the number of rotatable bonds. The maxcore parameter could be used to make a very approximate rough quick pass at docking. See Section 2 of the *FirstDiscovery Technical Notes* for details.

`corescale`
`Corescale` is a fractional value to scale down the default number of core conformations kept. See Section 2 of the *FirstDiscovery Technical Notes*.

`noringconf`
The `noringconf` keyword disables ring conformation generation.

3.6.12 Subtask Similarity

Request Glide similarity scoring.

Similarity scoring entails assigning a number to each ligand based on its similarity to one or more of a set of selected *active* ligands, and optionally (*weighted* or *calibrated* similarity) also its dissimilarity to a set of selected *inactive* or *decoy* ligands. Unlike most quantities calculated in Glide, similarity is a *ligand-based* rather than a *structure-based* property. That is, the similarity between two molecules depends only on the types and connectivity of the atoms in those molecules, and not on any details of their coordinates or conformations, or on anything to do with the receptor. Glide thus performs similarity scoring, if requested, just once per ligand. It therefore adds negligible overhead to a typical Glide database screening job, and may even speed it up because some ligands can be immediately rejected. Weight calibration adds a small amount of time to a grid generation job.

The similarity of one ligand (in the test set) to another (in the training set) is evaluated by comparing the set of all atom pairs in the test ligand to the set of all atom pairs in the training ligand. Within each ligand, each atom pair is characterized by the element types, bond orders, and formal charges of the two atoms, and the number of bonds in the shortest path connecting them. The similarity is normalized to a number between 0 (the two molecules have no atom pairs in common) and 1, in which case the molecules have all the same atoms with the same connectivities, and are thus either identical or stereoisomers of each other. For weighted similarity, each atom pair in the training set (actives) is assigned a weight factor, which is higher if the given pair appears more often in the actives and lower if it appears in the inactives.

To use similarity scoring, put `simil` subtasks in the grid generation (only for calibration in weighted similarity) and ligand docking tasks, following the meta-examples below. Glide will then adjust the Glidescore of each docked ligand pose by adding a term that depends on the maximum similarity of that ligand to any of the actives.

- `simil weight actives [maestro | sd] afile` *fname* -
  `inactives [maestro | sd] ifile` *fname* -
  `percent` *val* `wfile` *fname* `[allprint | noprint]`
- `simil actives [maestro | sd] afile` *fname* -
  `[wfile` *fname*`] -`
  `[penalty` *val*`] [lowsim` *val*`] -`
  `[highsim` *val*`] [reject` *val*`] [allprint | noprint]`
- `simil name` *spec*

The calibration step for weighted similarity is specified by the `weight` keyword. This step should be performed in a grid generation job, and all of the following keywords are *required*.

`actives [maestro | sd] afile` *fname*
: Specifies that the active ligands in the training set are in file *fname*, which may be in either Maestro or MDL SD format. Note that at least two active ligands are required for calibration.

`inactives [maestro | sd] ifile` *fname*
: Specifies the file containing the decoy ligands.

`percent` *val*
: Roughly specifies the percentage of the inactives to be included in weight calibration. Rather than using preselected ligands from the `inactives` file, each molecule in the file has *val* percent probability of being used in weight calibration. Thus, the number of ligands selected may not exactly match the user's `percent` input. Note that at least one decoy compound is required for calibration, and that a weight calibration job will exit if it has not read in at least two active ligand structures, and chosen at least one inactive. For best results, we recommend making the `inactives` file large enough, and the `percent` probability high enough, to use about 5 to 15 times as many decoys as actives. For instance, if the `actives` file contains 10 ligands and the `inactives` file contains 1000, use a `percent` value between 5.0 and 15.0. Weight calibration may produce a message stating that it did not converge (more likely the higher the ratio of inactives to actives), but this is not a problem: a valid weights file is produced in any case, and contains the "best" weights obtained with the given structures.

`wfile` *fname*
: Write the weights to the file *fname*. This will be a text file, with each line containing a symbolic representation of an atom pair, followed by the calibrated weight for that pair.

`allprint`
: The `allprint` keyword enables maximum printing of output from the similarity machinery including output of the similarity of each docked ligand to each probe molecule. Default printing outputs only the maximum simiarity of the docked ligand to any probe molecule.

`noprint`
: The keyword `noprint` disables printing of output from the similarity machinery.

To use similarity scoring in a ligand docking job, all that's required is the specification of an `actives` file. The `simil` subtask should appear in the first (setup) `DOCK` task of the job.

`actives [maestro | sd] afile` *fname*
: Adjust the Glidescore values for poses of each ligand according to the similarity of that ligand to those in file *fname*. This need not be the same file as was used for weight calibration in the previous grid generation job, even if the weights generated in that job are to be used.

`wfile` *fname*
: Use calibrated similarity, with weights taken from file *fname*.

`penalty` *val* `lowsim` *val* `highsim` *val*
: Parameters for adjusting Glidescores. If the maximum similarity between a given docked ligand and any ligand in the `actives` file is less than `lowsim`, add the full `penalty` value to the Glidescores of all docked poses of that ligand. If the maximum similarity is greater than `highsim`, do not adjust the Glidescores for that ligand. If the maximum similarity is between those two values, the Glidescore adjustment is determined by a linear ramp between the maximum `penalty` value and zero. Note that while `lowsim` must be less than or equal to `highsim`, there are no other restrictions on their values; in particular, they need not be between 0.0 and 1.0, even though all similarity scores will be in that interval. Choosing `lowsim` less than zero, for instance, simply means that the maximum `penalty` value will never be applied to any ligand. Also, `penalty` may be negative, in order to reward ligands that are *not* similar to any of the actives (to promote diversity, for instance). The defaults are `penalty 6.0 lowsim 0.3 highsim 0.7`.

`reject` *val*

Skip any ligand whose maximum similarity to any active ligand is less than *val*. Must be between 0.0 (accept all ligands) and 1.0 (skip all ligands that are not identical to or stereoisomers of one of the actives). Default is `reject 0.0`.

The third form of the `simil` command, `simil name` *spec*, should appear in the `DOCK` task for each ligand. (The first for that ligand, with `ligand name` *spec* rather than `ligand keep`.) It simply indicates that similarity scoring is to be applied to species *spec* (the current ligand), using the `actives` file (and weights, if any) read in the initial (setup) `DOCK` task.

3.6.13 Subtask Screen

Request screening phase of docking calculation.

- `screen noscore -`
  `[refine [refstep` *num*`] [maxref` *num*`] [refgreedy]]`
- `screen [scbsize` *val*`] [skipb` *num*`] -`
  `[maxkeep` *num*`] [scorecut` *val*`] -`
  `[readscreen` *fname*`] [writescreen` *fname*`] -`
  `[box center -`
  `[lig | read xcent` *val* `ycent` *val* `zcent` *val*`] -`
  `[boxxr` *val* `boxyr` *val* `boxzr` *val*`] -`
  `[ligxr` *val* `ligyr` *val* `ligzr` *val*`]] -`
  `[readcmsite` *fname*`] [writecmsite` *fname*`] -`
  `[greedy [fraction` *weight*`] [readgreed` *fname*`] -`
  `[writegreed` *fname*`]] -`
  `[refine [refstep` *num*`] [maxref` *num*`] [refgreedy]]`

`noscore` Do not perform rough-score calculations or screening on the current ligand. This keyword is needed when the `refine` step must be performed after a loop (either in DICE or internally) has already done screening on multiple (internally or externally generated) conformations. It is probably not useful otherwise.

`scbsize` The grid spacing, in Angstroms, of the rough-score grid. Default is `scbsize 1.0`.

`skipb` *n* Use only every *n*'th grid point in each direction as a possible site for the ligand center. Thus `skipb 2`, the default uses one-eighth of all grid points.

`maxkeep` Maximum number of poses to pass to the grid energy calculation. Default is `maxkeep 1`, but it's generally not useful to leave it at that. In our tests, we have found that a few hundred poses, over multiple conformations, are usually enough to find one or more

good docked poses, at least if *greedy scoring* and *pose refinement* are employed.

`scorecut` Rough-score cutoff for keeping poses. When accumulating poses to pass to the grid energy calculations (after they have passed all other screening tests), a given pose survives if its rough score is within `scorecut` of the best pose accumulated so far. Default is `scorecut 100.0`.

`readscreen`
`writescreen`
Read/write the rough-score grids (and possibly other information: see `readcmsite` below) from/to the indicated file. The file specified in a `readscreen` should have been written as the result of a `writescreen` in a previous run with the same receptor.

`writecmsite`
Write to disk information about possible grid sites for the ligand center, for those sites that pass an initial (ligand-independent) filter. This is generally a much smaller set than the entire box where the rough-score grid is defined, so Glide calculates it once for a given receptor and store the list on disk for subsequent use with different ligands. If `writecmsite` is not specified, this information is appended to the file specified in `writescreen`. Different `box` specifications, or different `skipb` specifications, result in different lists of sites, so we provide the option of writing these to separate files, without repeating the much larger rough-score grids in the `writescreen` file, which are independent of `skipb`.

`box` Specifies the rectangular box where the rough-score function is defined (*enclosing box*), and/or narrower limits on the position of the ligand center (*bounding box*). Default for the enclosing box is that specified in the `receptor` subtask for the energy grids, either by the `active` and `buffer` specifications or by a `box` specification in that subtask. The `box center` and `boxxr` specifications are as in the `receptor` subtask, with the additional option `box center lig` to put the center of the box at the coordinates of the ligand center in the input file. If the input is a known co-crystallized complex, `box center lig` biases the calculation in favor of the known correct answer, and should not be used except for testing. The parameters `ligxr`, `ligyr`, and `ligzr` give the size of the search space for positions of the ligand center. That is, the ligand center may be placed at grid points with x-coordinates between approximately `xcent`$-$`ligxr`$/2$ and `xcent`$+$`ligxr`$/2$, and similarly for y and z. In general, the bounding box should be much smaller than the

enclosing box, because grid points near the edges of the enclosing box will have many ligand atoms outside the box, and thus be rejected as possible ligand center positions. The Maestro user interface determines the size of the enclosing box (purple outline on the Maestro display) by adding to the user-specified size of the bounding box (green) a buffer big enough to fit ligands up to a user-specified size, when the ligand center is at the edges or corners of the bounding box. The limits on the ligand center position are incorporated in the grid file written by `writescreen` (or `writecmsite`), so `box ... ligxr ...` is unnecessary when reading existing grid files from disk `readscreen`.

`greedy` Specifies the greedy scoring algorithm, as described above. `fraction` *weight* specifies that the combination to use is *weight* times the score at the best surrounding grid point, plus (1 − *weight*) times the original score at the central point. The default is `fraction 0.33`, and acceptable values are between 0 and 1. `readgreed` and `writegreed` specify reading/writing the *greedy grid* (the linear combination at each point, not the best surrounding score) from/to the indicated file.

`refine` Specifies the *pose refinement* step of the screening algorithm. This involves moving each pose from its original central grid point to a 3 x 3 cube of surrounding grid points. Each point is either zero or `refstep` grid points away from the central one in each of the positive or negative x, y, and z directions, where `refstep` must be smaller than `skipb` (so as not to get to a position already tested for the ligand center), and the default is `refstep 1`. The algorithm evaluates the score of the pose centered at each of the 27 grid points (in the same orientation as the original), and chooses the best (lowest) score to pass to energy minimization. The refinement step improves the scores of poses that are close to favorable ones that were initially skipped because of the `skipb` specification, and thus often decreases the number of poses that need to be passed to energy minimization in order to assure that good ones are included. To decrease the number actually passed, specify `maxref` less than `maxkeep`. Since pose refinement and greedy scoring are both intended to find good scores that would otherwise be missed because of `skipb`, the default is for refinement to evaluate the 27 poses using the *original* (non-greedy) score, even if the rest of the screening process used the greedy score. The keyword `refgreed` specifies that refinement should use greedy scoring (if the greedy-score grid is available), but we have not found any advantage in doing this, and it runs the risk of increasing the rate of false positives.

3.6.14 Subtask Minimize

Request energy minimization phase of docking calculation.

- `minimize flex itmax` *num* `ftol` *val* `dielco` *val* `[ highacc [ ncycle` *val* `] ]`

`flex` Indicates that ligand torsional angles are to be varied during minimization.

`itmax` Maximum number of iterations of the minimization (conjugate gradient) algorithm. The default is `itmax 1000`. In our experience the minimizer always converges in many fewer steps than this (typically fewer than 50, and almost always fewer than 100), but the maximum should of course be set higher than the expected number. `itmax 0` does a single-point energy calculation on each pose that survives rough-score screening, or on the single initial pose if no screening was done.

`ftol` Convergence criterion for the minimizer, expressed as a bound on the relative energy change at the last iteration. The default is `ftol 1.0e-4`.

`dielco` The dielectric constant, or coefficient of the interatomic distance in the distance-dependent dielectric function, to be used in calculating electrostatic energies. Thus if `rdiel` is specified in the `receptor` subtask, and `dielco 2.0` is specified here, the dielectric used is $2r$. The default is `dielco 1.0`, but we recommend (and the Maestro interface writes) `dielco 2.0`, along with `rdiel`, to weaken long-range electrostatic interactions.

`highacc` This keyword activates Glide's *extra precision* mode, it directly corresponds to choosing "Extra Precision" in the Maestro Glide panel "Choose Docking Mode" pull-down selector.

`ncycle` *val*
This keyword is only available when `highacc` is also used, and sets the number of times the ligands are *recycled* through the docking process. This additional effort greatly improves Glide's ability to sample all the docking positions of the ligand in the receptor grid. The default value is 5.

3.6.15 Subtask Final

Specify final scoring function.

- `final [glidescore|noglidescore] [read` *fname*`]`

The `final` subtask specifies the scoring function to be used for final evaluation of the docking affinity of ligand poses. The recommended scoring

function is Schrödinger's proprietary GlideScore (tm). `final glidescore` should appear in the setup `DOCK` task, and in cases where receptor information is to be read from disk, the keyword-value pair `read` *fname* should appear in the `DOCK` tasks that do the scoring, to indicate the file that contains receptor information needed for calculating GlideScore. In general, the name of this file will be *gridjob*`.csc`, where *gridjob* is the name of the job in which receptor grids were created.

3.6.16 Subtask Scoring

Filters and parameters for final scoring.

`scoring ecvdw` *val* `hbfilt` *val* `metalfilt` *val* -
`hbpenal` *val*

The `scoring` subtask is useful for filtering out ligands, structures, or poses that might be assigned favorable GlideScore values, but are unacceptable for other reasons. The filters consist of maximum allowed values for the Coulomb plus van der Waals interaction energy calculated by grid interpolation (`ecvdw`), or the hydrogen-bonding (`hbfilt`) or metal-binding (`metalfilt`) terms in GlideScore. Poses that fail these filters are either skipped or assigned specific unfavorable GlideScore values such as 10000.0. Alternatively, the user may specify undemanding values (such as 0.0) for the filters in the Glide run, and impose more stringent filters in postprocessing, by running the `glide_sort` script, with the filter values among its arguments, on Glide's output structure files. This script allows not only filtering with a variety of criteria, but also re-sorting according to user-specified scoring criteria, without rerunning the Glide job.

The `hbpenal` parameter is not a filter, but rather the coefficient (default 3.0) of a term in GlideScore that penalizes poses in which potential hydrogen-bonding atoms are buried next to non-polar atoms in the ligand-receptor interface.

3.6.17 Subtask Report

Write final ligand structures and scores to disk, and/or copy coordinates back to top-level Impact arrays.

- `report setup [by glidescore | by energy] -`
  `[nreport` *num* `[cutoff` *val*`]] [norecep | recep | nil] -`
  `[external file` *fname*`] -`
  `[maxperlig` *num*`] rmspose` *val* `delpose` *val*
- `report collect rmspose` *val* `delpose` *val*
- `report rmspose` *val* `delpose` *val* -
  `write filename` *fname*
- `report keep [current | reference | best]`

The `report` subtasks specify how Glide is to select ligands and poses for output, and how to sort that output. In addition, the `keep` keyword specifies the ligand structure to copy internally, for use by subsequent (non-Glide) Impact tasks.

`setup` This version of the `report` subtask, with the following specifications, is required in the "setup" `DOCK` task, in order to allocate memory for the data to be saved and reported.

`by glidescore`
`by energy` Indicates whether the poses written to external files are to be those with the best `nreport` GlideScore or the best `nreport` grid energies (Coul `+` vdW). (`by score`, for the best `nreport` rough scores, is also available but not recommended.) The poses will be sorted in order of the selected scoring function.

`nreport` The maximum number of poses to be written to external files. The actual number written may be less than this either because fewer poses survive the rough-score or final scoring filters or because of the `cutoff` parameter.

`cutoff` Saves for output only those poses whose scores or energies are less than the best (lowest) plus the `cutoff` value.

`norecep`
`recep` Indicates whether the output structure file (in Maestro format) should include the receptor structure or not. The default is to include it (`recep`). If it is included, the file is suitable for on-screen analysis using the Glide *Pose Viewer*; otherwise (`norecep`), the file is suitable for use as ligand input in a subsequent Glide job. (Actually, files that do include the receptor may also be used in this way, simply by using the `gotostruct` keyword upon reading the file, to skip the receptor structure (which is always the first structure in the file).)

`external file`
Store qualifying poses from each ligand, as it is processed, in the specified file. The resulting file will in general be larger than the final output, as poses saved from one ligand may ultimately be displaced by better-scoring ones from subsequent ligands. But

this method saves both CPU time and system memory, and also provides a "checkpoint" file of results so far, in case the job fails in the middle of the run. Unfortunately, external file storage does not work for "score in place" jobs, or if the `confgen` option (flexible docking of internally generated conformations) is not selected. We strongly recommend its use in all other cases.

`maxperlig`
: Maximum number of poses to save for each distinct ligand molecule. `Maxperlig 1` is particularly appropriate for relatively rapid filtering of a large ligand database. The best-scoring ligands from such a run may then be used as input to a run with larger `maxperlig`, to get finer detail of binding modes, etc., of the top ligands.

`rmspose`
`delpose`
: Criteria for eliminating "duplicate" poses, i.e., those that are too similar for both to be worth saving. Two poses are considered distinct if they satisfy *either* the RMS deviation or the maximum deviation criterion. The recommended values are `rmspose 0.5 delpose 1.3`. These must be specified in every `report` subtask.

`collect`
: Store the data for poses to be saved from the current ligand. This version of the `report` subtask typically appears in a loop over ligand (and/or conformer) structures. If `external file` was specified with `report setup`, the qualifying poses are saved to the external file; otherwise, their scores and identifiers, and information needed for reconstructing their structures, are stored in memory.

`write filename` *fname*
: Write the saved poses, and a summary report, to disk, using *fname* as a base for the file names. The report will be written to *fname*.rept. If the receptor structure is included, it and the ligand pose structures will be written to *fname*_pv.mae (pv for Pose Viewer); if not, the ligand structures will be written to *fname*_lib.mae (a "library" of ligand structures for future use). If an "intermediate" `external file` was specified in the `report setup` subtask, Glide internally runs the `glide_sort` script (with filters as specified in the `scoring` subtask, and defaults for other arguments) on the intermediate file to get the

final output. For postprocessing, the user can run `glide_sort` on either the intermediate file or the final output file.

`keep` Specifies which coordinates to copy back to the main Impact coordinate arrays, for subsequent Impact tasks.

- `current` Do nothing. This maintains the Impact coordinate arrays as they were upon input to the current `DOCK` task.
- `reference` Copy the reference conformation (in its input pose) back to the Impact arrays.
- `best` Copy the best pose (by GlideScore or grid energy, as specified with `report by`) back to the Impact arrays.

3.6.18 Subtask Run

Run docking calculation as specified in previous subtasks.

- `run`

Run the calculation. No keywords because they're all specified in the previous subtasks.

3.6.19 Results printed to Impact output

In addition to the structural output and summary reports described above (Maestro format structures in '`*.ext`' and either '`*lib.mae`' or '`*pv.mae`'; summary reports in either '`*.rept`' or '`*.scor`'), Glide reports results for each ligand it processes to the usual Impact output, namely "standard output" (typically redirected to file '*jobname*`.log`') and the *main output* file (typically '*jobname*`.out`') specified in the `write` command at the top of the Impact input file. For each ligand processed, this output includes information on the best pose found according to each of several scoring criteria.

```
DOCKING RESULTS FOR LIGAND       1 (Atropine)
Best Glidescore=-6.24 E=-26.53 Eint=5.56, pose 277, conf 2, lig 1; rmsd=66.161
Best Emodel=-57.10 E=-43.85 Eint=2.10 Glidescore=-5.42, pose 16, conf 3, lig 1; rmsd=61.597
Closest rmsd=61.572, pose 57, conf 3, lig 1; Glidescore=-2.48 E=-43.70 Eint=2.02
Lowest Efinal=-43.99 Eint=1.99 Glidescore=-2.23, pose 17, conf 3, lig 1; rmsd=61.596
```

In each of the above output lines, `E` or `Efinal` is the minimized, grid-interpolated Coulomb + vdW interaction energy between the receptor and the ligand in the particular pose; `Eint` is the internal (torsional) energy for the particular Glide-generated conformation of the ligand, and `Emodel` is the combination of `E` and GlideScore that Glide uses to rank poses of the same ligand. `Rmsd` is the heavy-atom RMS deviation between the particular pose

and the reference ligand, and is reported only for the first ligand processed, and only if it is the same molecule as the reference.

In rigid docking runs, Glide groups together conformers of the same ligand that appear consecutively among its input structures. In such cases, the `DOCKING RESULTS` above are reported for the entire group, with an indication that all are conformers of one molecule.

```
DOCKING RESULTS FOR LIGANDS  57 --  58 (Confs of p38-pyrimidone0003)
Best Glidescore=10000.00 E=329.44, pose 1, conf 1, lig 57
Lowest Efinal=237.13 Glidescore=10000.00, from pose 9, conf 2, lig 58
Best Emodel=10000.00 E=237.13 Glidescore=10000.00 from pose 9, conf 2, lig 58
```

The values of 10000.00 in the above table indicate that Glidescore and Emodel were not evaluated for those poses, because they did not pass the filters specified in the `scoring` subtask. Note that `lig 57` and `lig 58`, and all ligand numbers reported in Glide output, refer to the position of the molecule in the user's input structure file. This correspondence is maintained not only for multiple conformers as above, but even if Glide cannot process some of the input structures. In other words, if the 56th structure in the input is skipped because it's too big, has unrecognized atoms, etc., the next structure will still be reported as ligand 57. Also, since this job did not generate ligand conformations internally, the designations `conf 1, lig 57` and `conf 2, lig 58` are actually redundant: the only conformations analyzed are those that were in the input, so `lig 57` *is* the first conformation of this molecule, and `lig 58` is the second.

In addition to the above output of "best" poses, Glide will print tables of poses processed from each ligand, after the rough-score and energy minimization steps, if the `verbosity` parameter is set higher than 1. Since this output can run to tens or hundreds of poses per ligand, we strongly recommend against setting `verbosity` that high in jobs with many ligands, except for testing or debugging purposes.

4 Analysis Routines

This chapter describes tasks for various analysis routines.

4.1 Task Analysis

Extract information about the molecular structure and energy. This task may be called at any time, provided the structural arrays are defined. `Energy` must be called after coordinates are defined and energy parameters are defined in `setmodel`. A number of example input files are included where `analysis` is used, for example

`geometry` (see Section C.2.9 [Geometry Analysis (example)], page 267).

`energy` (see Section C.2.8 [Energy Analysis (example)], page 266).

`rms` (see Section C.3.1 [RMS dev (example)], page 269).

`surface area and solvation energy`
(see Section C.3.6 [Area vs. Solv Energy (example)], page 304).

In addition to the keywords listed below, the subtasks of task `analysis` can take the optional keyword `echoon` or `echooff`. This controls the printing of certain output. The default is to print it (`echoon`), unless `echooff` has been specified either in this task or previously at the task level.

4.1.1 Subtask Energy

Calculate a potential energy function (as defined by `setmodel`) and print out detailed information about the energy terms. For examples of use see Section C.2.8 [Energy Analysis (example)], page 266.

- `energy allterms [ solvation [ of name` *species_one* `] [ by name` *species_two* `] -`
  `[ encut` *value* `] ]` *options*
- `energy [ bond | angle | phi | nb14 | noe | ljel | hbond ] -`
  `[ solvation [ of name` *species_one* `] [ by name` *species_two* `] [ encut` *value* `] ] -`

  options

where *options* is described by the following metaexamples:

- `highest` *num* `[ file` *fname* `]`
- `higher encut` *value* `[ file` *fname* `]`
- `res-res one name` *species* `-`
  `[ ngroup` *ngps* `( resnumber` *num* `)` repeated *ngps* times `]`
- `res-res between name` *species_one* `name` *species_two*
  `[ ngroup` *ngps* `name` *species* `( resnumber` *num* `)` repeated *ngps* times `]`
- `file` *input_file*

4.1.1.1 Energy terms

Energy terms to be analyzed.

- `energy [ allterms | specific_term ]`

`Allterms` specifies energy analysis for all energy terms. The other options are:

`bond`
`angle`
`phi`
`nb14`
`noe`
`ljel`
`hbond`

Note that the appropriate output file should be specified as soon as is feasible.

`highest` The number of energy terms to be printed, e.g., the "highest" 10 energy terms (violations). At most 50 terms of each type (bonds, angles, etc.) can be printed; requesting more than 50 will have the same result as requesting 50. Of course, if there are only 33 bonds in the molecule, only 33 bond terms will be printed even if you specify "highest 50."

`higher` Flag to print out all energy terms (violations) higher then `encut`.

`encut` Energy cutoff value.

`res-res` Print out the energy between all residues for a species.

`one` Option available only with `res-res` subtask. Only one species used.

`between` Print data between species specified as follows.

- `between name` *spec* `resnum` *num* `to` *num*

If the residues are to be grouped together, then print out data in terms of groups of residues as opposed to residue by residue. The keyword `ngroup` signals that starting and final residues of a group must be specified. Several groups may be specified in this way.

'`ngroup resnumber` *num* `to` *num*'

4.1.1.2 Solvation

Calculate the solvation energy for each atom in a given species.

`of name` The name of the species for which the solvation energy is to be calculated (the solute).

`by name` The name of the species to use as the solvent. The results are stored in the internal table '*hydration*' and may be used in advanced input scripting language (DICE) commands.

`scutoff` The cutoff distance . . .

Solute and solvent must be different species.

4.1.1.3 Analyze

Analyze the hydrogen bond energy by recalculating the electrostatics and the 10–12 term so that an accurate value for a hydrogen bond energy is calculated (including the angular dependence). Distance (`hbcut`) and angle (`hbangcut`) cutoffs may be specified (defaults are 4.0 Å and 120.0 degrees).

- `energy analyze hbond [ hbcut` *value* `] [ hbangcut` *value* `]`

4.1.2 Subtask Qmme (QMMM)

Single point QM/MM energies can be obtained using task ANALYSIS with the subtask `qmme`, e.g.:

```
ANALYSIS
  qmme
QUIT
```

`qmme` requests a QM/MM energy calculation. QSite jobs launched from Maestro will evaluate the MM energy regardless of whether or not it is a minimization job, and therefore this keyword is not needed for Maestro created input files.

4.1.3 Subtask Measure

Calculate internal coordinates. The `measure` subtask is unusual in being terminated with the keyword `quit`, making it somewhat like a task. As with the `setpotential` subtask of the `setmodel` task, which is also terminated by `quit` (see Section 2.3.4 [Subtask Setmodel], page 41), this means that each `monitor` or `calc` option must be on its own line. An example of the syntax is as follows.

```
ANALYSIS
  measure name spec [results file fname]
    calc [options]
  quit
QUIT
```

Tha default option is to use x, y, z coordinates that already exist (previously defined by `create`, `montecarlo`, `dynamics`, etc.) and to calculate only those internal coordinates explicity user-defined.

The options available with this subtask are as follows.

- `monitor nskip` *number* `statistics`
- `calc [ allinternals | sidechain ] resnumber` *resn* `atomname` *atna* `[ pdb file` *fname* `]`
- `calc bond ( resnumber` *resn* `atomname` *atna* `)` two times `[ pdb file` *fname* `]`
- `calc angle ( resnumber` *resn* `atomname` *atna* `)` three times `[ pdb file` *fname* `]`
- `calc torsion ( resnumber` *resn* `atomname` *atna* `)` four times `[ pdb file` *fname* `]`

1. Arbitrary user-defined bonds, angles, or torsions are calculated between any atoms (whether or not they follow the *tree structure* or are bonded).
2. All internal coordinates as defined in `create` (the *tree structure*) are calculated.

These coordinates are calculated from atomic positions already existing within an Impact job, or from a coordinate set read in from an external PDB file.

4.1.3.1 Calc

Flag to calculate internal coordinates. If the `calc` option is chosen, multiple `bond`s, `angle`s, and `torsion`s can be calculated within the same command line. However one must `quit` from a `measure` session and call it again before `calc all` or `calc sidechain`.

The `calc all` exactly calculates the internal coordinates as defined by the `tree`, thus no improper dihedral angles will be calculated, and some desired angles may also be missing.

When defining `torsion`s be sure the order of the four atoms is the same as the order used in the parameter file to define the desired torsional constant. Else, the dihedral angles calculated will be for a different angle. (e.g. `phi` (1, 2, 3, 4) is different from `phi` (1, 2, 4, 3) for atoms 1, 2, 3 and 4).

`allinternals`
: calculate a list of all internal coordinates defined by the tree structure in `create`.

`bond`
: Calculates the distance between two atoms specified by two sets of parameters: residue number; atom name. Atoms need not be bonded.

`angle`
: Calculates the angle between three atoms specified by three sets of residue number; atom name parameters. Atoms need not be bonded or follow tree structure.

`torsion`
: Calculates the torsion angle between four atoms specified by four sets of residue number; atom name parameters. Atoms need not be bonded or follow tree structure.

`sidechain`
: Calculates all torsions along side chain of the residue specified by parameter `resn`, torsions follow tree structure.

`results file`
: Specifies that an output file is being given for these results. If this is not specified, the results are written to the main output file.

4.1.3.2 Monitor

Monitor a series of internal coordinate measurements, instead of only calculating one set of internals.

`nskip` Indicates that every `nskip`th configuration will be `measure`d.

`statistics`
: Calculate the average and r.m.s. for each internal coordinate that is `monitor`ed.

4.1.4 Subtask NOE

This option will print distances between H atoms that are between upper and lower bounds given. Intra-residue interactions are not considered. These distances can be used to simulate those that would be expected to give NOE peaks in an NMR experiment. There is an option to assume all `prochiral` assignments can be made. This subtask can be used to generate a preliminary constraint file that can be used in other simulations or to compare two coordinate sets.

- `noe name` *spec* `ucut` *value* `lcut` *value* `[ gen file` *fname* `] -`
  `[ lcut` *value* `] [ ucut` *value* `] [ plus` *value* `] [minus` *value* `] [ prokiral] [ pdb file` *fname* `]`

`ucut` Upper distance limit to consider for possible NOE peak. The default value is 4 Å.

`lcut` Lower distance limit to consider for a possible NOE peak. The default value is 1.2 Å.

`gen` Flag to indicate that a constraint file is to be generated from the above list.

`file` Name of constraint file.

`plus` Amount added to calculated distance to generate upper bound.

`minus` Amount subtracted from calculated distance to generate lower bound.

`prokiral` Make all prochiral assignments

`pdb` Coordinates may come from file *fname*

4.1.5 Subtask Hbond

Print distances between H-bonding donor and acceptor atoms that are between the distance `cutl` and `cutu`. H-bond angle criteria are not considered. For DNA this option will only print out H-bonds between the bases.

- `hbond name` *spec* `cutu` *value* `cutl` *value* `[ gen file` *fname* `] -`
  `[ pdb file` *fname* `]`

`cutu` Upper distance limit to consider for a possible `hbond`. The default value, if this parameter is not specified, is 4.0 Å.

`cutl` Lower distance limit to consider for a possible `hbond`. The default value, if this parameter is not specified, is 1.2 Å.

`gen file` Flag to indicate that a constraint file is to be generated from the above list.

`plus` Real amount added to calculated distance to generate upper bound.

`minus` Real amount subtracted from calculated distance to generate lower bound.

`pdb` Coordinates may come from this PDB file.

4.1.6 Subtask Neighbor

This option will print distances between atoms that would be in "close contact" as defined by the user.

- `neighbor [ name` *spec* `] [ resn` *num* `] [ atna` *atom_name* `] -`
  `[ cutu` *val* `] [ cutl` *val* `] [ rsep` *num* `]`

`resn` Residue number atom `atna` is found in.

`atna` Atom name of atom to search for neighbors.

`rsep` Minimum residue separation

0 will print neighbors in the same residue

1 will print neighbors in adjacent residues, etc.

`cutu` Upper distance limit to consider for a possible close contact. The default value, if this parameter is not specified, is 4.0 Å.

`cutl` Lower distance limit to consider for a possible close contact. The default value, if this parameter is not specified, is 1.2 Å.

4.1.7 Subtask Rms

Calculate the RMS deviation in atomic positions between two trajectory frames or two conformations of a molecule according to the algorithm of Ferro & Hermans (*Acta Cryst.* 1977 **A33**, p. 345). The structural information may be passed from `task create`, or a PDB file can be read in directly. Residue names, atom names etc. will be either passed from another task or taken from the first PDB file read.

If the internal coordinates and connectivity are *not* passed from another `task`, `pdb1` must be the first command argument. Otherwise, the command arguments may be in any order.

Caution: `rms` does not work with structures read via `type auto`, e.g., Maestro files.

- `rms [ name` *species1_name* `] [ pdb1 file` *fname* `] -`
  `[ name` *species2_name* `] [ pdb2 file` *fname* `] -`
  `[ compare [ all | same | read [bone] | bone ] ] [ hand rev ] -`
  `[ nseg` *nrng* `(fres` *num* `lres` *num*`)` repeated *nrng* times `] [print none ]`

`pdb1` Name of PDB file if internal information is not being passed. System size will be determined by this PDB file, or data passed from another Impact task. Use of this parameter allows the task to be used independently of other Impact tasks by reading in a PDB file directly.

`pdb2` Name of PDB file to compare. This file must have the same `residue` names, `atom` names etc., as the original data. **Caution:** any atoms in this file, not present in `pdb1`, will be omitted in the calculations.

`compare`

- `all` First system. Atoms *must* be in the same order, and both systems *must* have the same total number of atoms. This option is the most efficient, however no checks are made and results will be strange if the above conditions are not met.
- `same` To compare each atom in the second system that has a corresponding atom in the first system.
- `read` To read in a list of residues to compare, using the `nseg ...` format shown in the command syntax.
- `bone` To compare backbone atoms only (N, C_α, C, O).

`hand rev` To compare systems with handedness reversed.

`nseg` Number of residue ranges to be read in and compared, with `read` option. The ranges are specified by a list of `fres` *num* `lres` *num* pairs indicating the first and last residues in each range.

`bone` When used with `read` option, allows for the comparison of backbone only of residues read in. Note that the keyword `bone` must come AFTER `read`, or else it will override `read` and lead to backbone comparison for all residues.

`print none`
Turn off all printing (none is required) but the final rms for all segments specified

4.1.8 Subtask Surface

This option allows the user to calculate the solvent accessible surface area of a molecule as defined by Lee and Richards (*J. Mol. Biol.* (1971), **55**, p. 379). The default resolution for the calculation is 0.25 Å.

- `surf name` *spec* `[ rprobe` *value* `] [ output` *fname* `] -`
  `[ read` *fname* `] type [ noh | h ] [ noprint ]`

`output` Directs the output from the program to a file specified by the user. Otherwise, the output will be directed to the main output file.

`rprobe` Changes the probe radius—default is 1.4 Å.

`type` This option directs the program as to whether or not to perform the calculation using hydrogen atoms (default) or NOH—without hydrogen atoms (extended atoms). The results from these two methods are similar, but often the literature values may reflect only one of the methods.

`noprint` Suppresses printing of surface area per atom.

4.1.9 Subtask Tormap

Produce data that can be used to plot 1- or 2-dimensional energy contour maps. Both sidechain and main-chain dihedral angles may be rotated independently or in any combination desired. The energies may be examined in several different ways. The output meta file contains contour maps of the torsional energy and is formatted into separate sections that correspond, e.g., to (1) the total potential energy, (2) the torsional energy, (3) the Lennard-Jones energy, (4) the electrostatic energy, and (5) the hydrogen bonding energy. (**Please Note:** This depends on the potential chosen in `setpotential`). The torsional angle term energies are also printed. An example of the use of `tormap` is shown in Section C.3.2 [Torsion map (example)], page 270.

`Tormap` type (`1d` or `2d`) must always be specified!

- `tormap 2d [ name` *spec* `] -`
  `tor1 res` *num* `[ main | chi ]` *angle_type* `[atom` *atom_name*`] init` *num* `-`
  `final` *num* `incr` *num* `-`
  `tor2 res` *num* `[ main | chi]` *angle_type* `[atom` *atom_name*`] init` *num* `-`
  `final` *num* `incr` *num* `-`
  `plot file` *fname* `title` *a_title* `contour 5 auto`
- `tormap 1d name` *spec* `-`
  `tor1 res` *num* `[ chi | main ]` *angle_type* `init` *num* `final` *num* `incr` *num* `*`

`1d` Used to specify the type of map, i.e., whether an energy map will be 1-dimensional.

`2d` For a 2-dimensional map.

`tor1` Specifies the first torsion angle. `tor1` and `tor2` specify which torsion angle parameters are to be used for each specific torsion angle. (Necessary for doing sidechain/main-chain maps).

`tor2` Specifies the second torsion angle.

`res` Residue number of interest

`chi` Specifies that the dihedral angle is a side-chain. The associated atom type indicates which side chain angle to vary

`main` Specifies the backbone dihedral angle of interest. Values: $\phi = 1$, $\psi = 2$, $\omega = 3$, other=4.

`atom` Specifies the atom name that defines the main chain torsion of interest when *angle_type* 4 has been chosen. The torsion angle varied is determined by tracing back the tree structure along the main chain.

`initial` Initial value of interest (default = 0°)

`final` Final value of interest (default = 360°)

`incr` Increment by which the angle is rotated (default = 5°).

Caution: The maximum number of steps is limited to the final-initial values (with `incr` = 1), however the number of steps should really not exceed 73 to maintain computational efficiency.

Example:

```
tormap 2d name dileu -
  tor1 res 2 main 1 init 0 final 360 incr 5* -
  tor2 res 2 chi 2 init 0 final 360 incr 10* -
  plot file enertor.out title phi vs chi1 in dileu * -
```

```
  contour 5 auto

tormap 1d name diphe -
tor1 res 2 chi 2 init 0 final 180 incr 5*
```

4.1.10 Subtask Violation

Analyze the residual violations of a distance constraint set. This option can only be invoked *after* reading in a constraint set through `setpotential`.

- `violation name` *spec* `cutoff` *num* `file` *fname*

`name` Molecular species name.

`file` Output file name.

`cutoff` Number of violations to be printed.

4.1.11 Subtask Potfield

This subtask produces and writes arrays of either electrostatic potential or electrostatic force-fields at a 3-dimensional grid of points, `epot`(x, y, z) (potential), or `xfield`(x, y, z), `yfield`(x, y, z), or `zfield`(x, y, z). These are plotted or written for use with graphics routines. See Section C.3.3 [Trajectory (example)], page 275 for an example where this subtask is used.

Caution: Subtask `potfield`, like subtask `measure`, is terminated by the keyword `quit`. The first occurrence of `quit` exits from the `potfield` subtask. A second occurrence of `quit` leaves the `analysis` task.

4.1.11.1 Grid

This keyword sets up the x, y, z grid points at which the potential and field are to be calculated. (It also finds the desired origin). The grid origin (point $0, 0, 0$) is at the center-of-mass of the entire system: a species, a residue, or an atom according to the specification.

- `grid [ center name` *spec* `[ resn` *residue* `[ atomname` *atna* `] | nil ] ] -`
  `[ boxsiz` *val* `] [ stepsiz` *val* `] chgcut` *val*

`Boxsize` is the size of the cubical box of grid points, with a default of 4.0 Å. `Stepsize` is the distance in Angstroms between adjacent grid points, with a default of 0.1 Å.

`Chgcut` is the radius in Angstroms from the origin for charge cutoff; only charges within `chgcut` contribute to the potential and field calculated at the grid points (molecular or atomic cutoffs as defined in `setmodel`). The default value is 5.0 Å.

4.1.11.2 Include

This keyword indicates which species are to be included in the calculation, i.e. the charges of the included species add to the electrostatic potential and field if they are within the radius `chgcut` of the origin. (If no species are included, then the resultant potential is everywhere 0.0). If all species are included then the keyword `all` is used, and individual species are specified as `name` *species_name* multiple times.

- `include [ all | ( name` *spec* `)` repeat up to all species `]`

4.1.11.3 Read

This optional keyword allows molecular coordinates to be read in from an external file; by default the molecular coordinates are the internal x, y, z values at the time `potfield` is called. It is possible to read a trajectory file containing many coordinate sets, in which case the output potential and field will be averaged over all the sets. For a description of the *trajectory-info* input options, see the syntax of the `input trajectories` command in Section 4.2.1 [Input (mdanalysis)], page 166.

- `read` *trajectory-info*

4.1.11.4 Rotate

This optional keyword allows molecular coordinates to be rotated so that the three reference atoms are in the yz plane. The reference atoms defining the rotation are expected to be in the same residue, and are specified by `atom` followed by three atom names, which must be the same as defined in the database . The default is to use atom numbers 1, 2 and 3. `Rotation` should be performed before `run`.

- `rotate resn` *residue* `atom` *atomname1 atomname2 atomname3*

`atom` *atomname1* defines the atom number at the plot origin; it should be the same atom that was defined by `grid center` to be the local origin. *atomname2* defines the atom number along the z-axis; i.e., $r_2 - r_1$ defines the z axis; and *atomname3* defines the atom number for the yz-plane, i.e., $(r_3 - r_1) \times (r_2 - r_1)$ defines the x-axis, thus atom positions r_1, r_2, r_3 are on the yz-plane.

4.1.11.5 Run

This keyword actually causes the calculations to be performed. The keyword `epot` causes calculation of the `potential`; this is the default. `Efield` causes calculation of fields (not done by default.)

- `run [ epot | efield ]`

4.1.11.6 Analysis

This keyword calculates the max, min, mean and rms values for the previously calculated data points. Note that this keyword must come after `run` or else the results will be meaningless.

- `analysis`

4.1.11.7 Plot

This keyword selects a grid slice for a 2-dimensional contour plot. The commands for plotting must all be input on the same line (see Appendix B [Plot], page 231).

- `plot [ epot | xfield | yfield | zfield ] -`
  `make [ x | y | z ] =` *val* `-`
  `title` *string* `* xlabel` *string* `* ylabel` *string* `* -`
  `contour` *contour_info*

`epot` Plot the coulombic potential;

`xfield`
`yfield`
`zfield` Plot the gradient of the potential (electric field) in the x, y, and z directions respectively;

`make` chooses the axis that is perpendicular to the plot slice, and its value (*cc*) at the intersection with the plane, as in '`make y = 2.0`', which means an xz slice that passes through the y axis 2.0 Å from the origin. The default is 0, i.e., the center of the box.

Example:

- `plot epot make x = 0.0`
- `plot xfield make y = -1.5 -`
  `title this is an electrostatic field plot * -`
  `file xzcontour.ts level3d theta 65.0 phi 60.0`

4.1.11.8 Grwr

This keyword is used to give the filename for the output of grid points, and causes the full grid to be output where `unformatted` is the default. Note that this causes the full 3-dimensional box of electrostatic (and x, y, z) datapoints to be written to the external file so formatted files will usually be very long. In contrast the `writ` keyword in the `plot` subtask causes only the 2-dimensional slice of datapoints that are being plotted to be written to the external file.

- `grwr file` *fname* `[ formatted | unformatted |` nil `]`

4.1.11.9 Grrd

This keyword causes the full grid of data to be read in where the default is `unformatted`. Note that data on `boxsize`, `gridsize`, etc., that are read from the *infile.dat* file take precedence over the equivalent keywords in the main input file.

- `grrd file` *fname* `[ formatted | unformatted |` nil `]`

4.2 Task Mdanalysis

Carry out a standard analysis of the trajectory produced by a molecular dynamics simulation.[1] The analysis may be one of two types, static and dynamic. An example of this task is shown in Section C.3.4 [MDanalysis (example)], page 284.

- Static analysis includes the site-site radial distribution function (`rdf` or $g(r)$), the binding energy distribution function (`bed`), the angular distribution function (`adf`) and the hydrogen bond distribution function (`hbd`).
- Dynamic analysis includes the mean square displacement (`msd`) for solvent, the velocity autocorrelation function (`vcf`), the angular velocity autocorrelation function (`avcf`), and the mean squared displacements (`msqdelr`) about the average position for each solute atom. The power spectra of `vcf` and `avcf` are also calculated.

4.2.1 Subtask Input

Control the reading of the trajectory files (how many records, how often, etc.) and set some options used in the analysis. The following qualifiers control the reading of the trajectory files, and they must all be given in a single command line.

- `input trajectories nfiles` *number* `fnames file` *fname* `file` *fname*`...` `-`
  `[ coordinates | and velocities |` nil `] [ every` *number* `] [ maxrec` *number* `] -`
  `[ nskip` *number* `] [ msteps` *number* `] [ box | nobox |` nil `] -`
  `[ recordno ] [ beginat` *number* `] [ to` *number* `] deltat` *value* `-`
  other_qualifiers_for_input

4.2.1.1 Trajectories

Read `nfiles` trajectory files, the list of files begun by `fnames`, and each filename preceded by `file`. Also describes how the trajectories are to be read. Note that if neither the `recordno` or `beginat` option is selected then all records are read sequentially from the first record of the first file.

`nfiles` Number of trajectory files to read.

`fnames` Begin the list of names of trajectory files.

`maxrec` Maximum number of trajectory records (frames) to be read. The reading of records will continue until `maxrec` records have been read or the end of file occurs, whichever comes first. Note that this need not be equal to the actual number of frames in the trajectory file.

[1] See Section 3.2 [Dynamics], page 77.

`nskip` Number of steps to be skipped over (the trajectory file will be sampled every `nskip` steps).

`coordinates`
[and `velocities`] [`every`] This option controls whether the (cartesian components of the) velocities are read (see Section 3.2 [Dynamics], page 77). The *number* after `every` should correspond to the way the trajectory file was written, that is, every *number*th step of the original simulation.

`deltat` Time step in picoseconds for each step of the MD run.

`box, nobox`
Specify whether the trajectory file contains dimensions of the box for each input frame. These dimensions are needed when processing constant-pressure simulations.

`recordno` The record number from each trajectory file to be read. If this option is set to zero (or not read) then reading of blocks of files may be specified with the next two qualifiers. This option allows only 1 record per file to be read.

`beginat` Beginning record to read from each file.

`to` End at this record in each file. If the `to` option is not specified then `maxrec` is used as the last record to be read (this would include all files). `nskip` is still active when the `beginat` option is used.

4.2.1.2 Other qualifiers for input

The following qualifiers are passed as options to the analysis routines.

`rup` Upper bound of distance r for radial distribution function $g(r)$.

`rlow` Lowerbound of distance r for radial distribution function $g(r)$.

`ngridr` Number of grid points in distance r for radial distribution function $g(r)$.

`eup` Upper bound of energy for binding energy distribution $bed(E)$.

`elow` Lower bound of energy for binding energy distribution $bed(E)$.

`ngride` Number of grid points along energy axis.

`ngridt` Number of grid points along time axis.

`ngrida` Number of grid points along angular axis.

`dw` Grid width of frequency axis in the power spectrum plot. (1/psec) (number of grid points along frequency axis is fixed at 100).

`nehb` Number of hydrogen bond criteria. If `nehb`=0, the `hbd` calculation is skipped. If `nehb` $\neq 0$, a file that includes hydrogen bond criteria must be opened by the `file` subtask.

`msteps` (For time dependent properties.) The maximum number of time steps to be used. This needs to be less than or equal to the number of records in the trajectory file.

4.2.2 Subtask File

Open and close I/O files. Only a few qualifiers are interpreted in this subtask.

- `file [ result | hbond ] file` *fname*
- `file close`

`result` Open the file *fname* where the results will be written out, rather than to the main output file.

`hbond` Open the file *fname* from which the hydrogen bond energy criteria (in kcal/mol) are read.

`close` Closes all the open trajectory files.

4.2.3 Subtask Static

Perform analysis of static properties for species-species interactions. The static properties that can be calculated within this subtask are: `rdf`, the radial distribution functions (and energy distribution functions), and `adf`, the angular distribution functions.

4.2.3.1 Rdf

Calculate the radial distribution (*rdf*) and energy distribution (*bed*) functions. The user must specify a pair of atoms (or groups of atoms) using `iatom` and `jatom`. An example of this subtask is seen in Section C.3.5 [RDF (example)], page 296.

For each group of atoms to be used, species, residues and atoms may be specified. The keywords `iatom` and `jatom` initiate the descriptions of the atoms to be included in the calculation; the input format is the same as in the `adf` calculation. The user must supply atom names (or groups of atom names) (i, j) after `iatom` and `jatom`. If the keyword `jatom` is followed by nothing then the choices for `iatom` are used. The names must be consistent with `igraph`. (see Section 2.2.3 [Create Subtask Print], page 33

for the definition of `igraph`). Unlike the `adf` case, all atoms entered after each keyword are regarded as non-equivalent. However, the user may also indicate what atoms are to be considered `equivalent` for the purpose of computing inter-molecular correlations. For example, a water molecule has two equivalent hydrogen atoms. In principle, any atoms in any residue can be declared `equivalent` to see the average over those atoms.[2] Atom names (after keyword `equivalent`) in a molecule must be consistent with `igraph` (see Section 2.2.3 [Create Subtask Print], page 33 for the definition of `igraph`). The sequences of atom names following `atom` and `equivalent` are terminated by the token `end`.

- `static rdf iatom name` *spec* `[ inresidue` *number* `| iresidue` *residue_label_type* `] -`

  `atom` *list_atom_names* `end [ equivalent` *atom_name atom_name* `end ] -`
  `jatom [ name` *spec* `[ jnresidue` *number* `| residue residue_label_type ] -`
  `atom` *list_atom_names* `end [ equivalent` *atom_name atom_name* `end ] ]`

- `static rdf run [` *plot_options* `[ delay file` *fname* `[ file` *fname* `] ] ]`

`iatom`

`run` Run the statics analysis. This takes a number of options for output.

- `wrrdf` Print out the radial distribution function rdf.
- `wrbed` Print out the binding energy distribution function bed.
- `wrhbd` Print out the hydrogen bond distribution function hbd.
- `plrdf` Plot rdf using the standard Impact plot options. For each radial distribution function two plots are generated: the `rdf` and its integration. Therefore, this option required that two file names be supplied to redirect the output of the graph (or any permitted device style – see Appendix B [Plot], page 231).
- `plbed` Plot bed.

[2] Physical interpretation of the result must, however, be made very carefully.

4.2.3.2 Adf

Calculate the angular distribution function *adf* for an atom triplet (*i*–*j*–*k*). Atom i is in one molecule; atom k is in the other molecule; atom j can be in either the first or second molecule (default is in first molecule which is a solute). The distribution for the cosine of the angle between the two vectors r_{ij} and r_{jk} ($r_{ij} = r_j - r_i$, $r_{jk} = r_k - r_j$) is calculated.

The keywords `iatom`, `jatom` and `katom` initiate the descriptions of the atoms to be included in the calculation. The user must supply atom names (or groups of atom names) (i, j, k) after key words `iatom`, `jatom` and `katom`. The names must be consistent with `igraph`. (see Section 2.2.3 [Create Subtask Print], page 33 for the definition of `igraph`). Atom name entry is terminated by placing `end` at the end of the list. Unlike the rdf case, all atoms entered after each keyword are regarded as equivalent.

By default all residues (keyword `all`) in the named species will be considered. Optionally, a specific residue number (`nres`) or a residue name (`res`) may be given. Unique atom names must always be input, as defined in `create`; the atom names must be placed after the keyword `atom`. All atoms entered after each keyword are regarded as equivalent.

Notes:

1. If a residue number (`nres` *res_number*) is supplied, the program calculates the adf of solvent around the specified atoms in that one residue. If a residue name (`res` *res_name*) is specified, then the adf of solvent around specified atoms in all residues with that specified name are calculated. If `all` is entered as a residue name, then the `adf` is calculated over all residues that contain the specified atom name(s).
2. The `adf` is only calculated for those solvent atoms that are between the values specified by the `rlow` and `rup` keywords. The cutoff is atomic or molecular as previously defined in `setmodel`. Typically the solute is atomic and the solvent molecular.
3. The cutoff radii (`rlow`, `rup`) used for `rdf`s are always atomic, even if the species has a molecular cutoff defined above. (See subroutine `dfunc` for exact code). Thus if angular are to be compared with radial distribution functions (`adf` and `rdf`), the former should also be calculated with atomic cutoffs. This is especially important for water hydrogens at small radii.

`bond` By default the `jatom` is bonded to the `katom`. The program makes the assumption that atoms that are bonded to each other have no distance cutoff to each other and that they are always in the same molecule. For atoms that are not bonded `rlow` and `rup` are used to determine if that pair of atoms is included in the `adf` calculation.

- `static adf bond` *iatm jatm katm* `to` *iatm jatm katm*

`nobonds` `iatom`, `jatom` and `katom` are not bonded to each other. This means that the three atoms are treated as isolated points. Cut-offs are used for each pair of atoms.

`oopl` Out-of-plane calculation.

- `static adf oopl [` *atomclass* `] [ morethan` *xc*1 `] -`
  `[ morethan` *xc*2`] ... from -`
  `[ name` *spec* `] [ resn` *number* `] -`
  `atom [` *iiatm jjatm kkatm* `end ]`

`oopl` calculates the number of atom(s) of type *atomclass* (i.e. of type `iatm`, `jatm`, or `katm` as defined above) that are more than distance `xc` from the plane defined by atoms `iiatm`, `jjatm` and `kkatm`, and also are within the radius limits `rlow` and `rup` (defined in `input`).

Caution:

1. If `oopl` is to make sense, then the atom types `iatm`, `jatm`, and `katm` need to have been previously defined, i.e., the line

   ```
   static adf name ...
   ```

   should come before the line

   ```
   static adf oopl ...
   ```

2. If `oopl` is to make sense, then one of the atom types that defines the radial cutoff (e.g. `jatm`) should also be one of the atoms that defines the plane (e.g. `jjatm`).
3. Up to ten `oopl` distances are allowed, each is preceded by the word `more` (or `morethan`) in the input line.
4. if `oopl` is used, then all atomic coordinates are rotated relative to the plane defined by `iiatm`, `jjatm`, `kkatm`; hence the usual periodic boundary conditions no longer apply. thus if periodic boundary conditions are used, and one is using a large `rup` (i.e., molecules near the boundary are being considered), then a normal angular distribution function or radial distribution function will be incompatible with an out-of-plane `adf` (i.e., don't calculate both in the same job).

`run` Run the statics analysis.

`wradf` Print out the `adf`.

`pladf` Plot `adf`.

4.2.4 Subtask Dynamics

This subtask analyzes "dynamic" properties.

4.2.4.1 Solvent

Calculate solvent properties.

`vcf` Calculate velocity auto-correlation function and its power spectrum.

`avcf` Calculate angular-velocity auto-correlation function and its power spectrum.

`msd` Calculate mean square displacement.

`plvcf` Plot `vcf`.

`plavcf` Plot `avcf`.

`plspectrum`
Plot power spectrum.

`wrvcf` Write `vcf` on specified file.

`wravcf` Write `avcf` on specified file.

`wrspectrum`
Write power spectrum on specified file.

4.2.4.2 Solute

Calculate solute properties.

`sqdelr` `sqdelr` is similar to `solvent msd` in calculating the mean square displacement, however it calculates atom by atom. The atomic mean squared displacements are only meaningful if the center-of mass is not moving.

4.3 Mini-Tasks: Nmodes and Rraman

The tasks `nmodes` and `rraman` are very small tasks that are not terminated by the keyword `quit`; however, they are placed just before the `end` that terminates the input file.

4.3.1 Task Nmodes

`Nmodes` will print frequencies and the associated mass-weighted cartesian normal modes *and* internal coordinate normal modes. If the following command line specifies `ped`, a potential energy distribution analysis will be calculated and printed. An example of the use of task `nmodes` is given in Section C.3.10 [Normal modes (example)], page 313.

```
• nmodes
  ped
end
```

Caution:

1. You should minimize the coordinates before a normal mode calculation. The results are completely meaningless if you do not minimize to a very strict tolerance on the energy and forces.
2. Caution must be used with `ped`. This routine requires an independent set of internal coordinates, which are assumed to be the first $N-1$ bonds, $N-2$ angles, and $N-3$ dihedrals; this requires the user to make sure that these degrees of freedom are independent in the residue file for building the molecule. Rings may be a problem if you are not careful; you may have to write your own routine to specify the internal coordinates.
3. You may find it helpful to print out an internal coordinate tree (see Section 2.2.3 [Create Subtask Print], page 33) so that the internal coordinate numbers specified in the `ped` analysis can be understood.
4. Both `nmodes` and `ped` have been rigorously tested for one species only. While the program has been set up to do more than one species, it should not be used for the case of two species, where it has not been tested. `Nmodes` cannot do a subset of atoms in one or more species.

4.3.2 Task Rraman

Resonance Raman (`rraman`) is a two-photon process involving transitions between the ground state and excited electronic states of a molecule. The matrix method approach to the calculation of optical absorption spectra assumes that the ground and excited states can be described in the harmonic approximation. In this method one writes the Hamiltonian for the excited electronic state in the (electronic) ground state basis and keeps only the

quadratic terms:

$$H_e = \frac{1}{2}\left(\vec{x}\cdot\mathbf{B}\cdot\vec{x} + \mathbf{K}\cdot\vec{x}\right)$$

where $\vec{x}$ represents the nuclear configuration written in terms of ground state modes; the matrix $\underline{\underline{B}}$ takes into account both the frequency shifts and mode-mixing that occur when the excited state modes are written in the ground state basis; and the vector $\underline{K}$ gives the displacements of the excited state configuration relative to the ground state one. We can use Impact to obtain the parameters $\underline{K}$ and $\underline{\underline{B}}$.

- `rraman`

  `ground coordinate file` *fname* `[print | noprint |` nil`]`

`end`

4.4 Table

This task provides some special functions for manipulating lists,[1] for looping over trajectory files, and performing several task-like subtasks.

4.4.1 Subtask Create

This subtask creates a new blank or filled table whose structure is defined in size and type by a template table.

- `create copy of` *list_expression*
- `create as [ empty | value` *user_constant* `]`

`as empty` Fill all the fields with zeros or blanks.

`as value` Set value to a user defined constant, such as a single number or a set of numbers or character strings (strings must be delimited by dollar signs).

`copy` creates a copy of a list expression. The list expression is normally a simple list, but it can be a series of values or a colon notation expression.

4.4.2 Subtask Print

This subtask prints tables indexing and labeling the entries in a meaningful manner. Tables that are of type `atom`, `residue`, or `species` will be indexed appropriately. Tables that are of the `bondlist`, `anglelist` or `torsionlist` type will be indexed with additional columns of atom and residue information. All other tables are printed with no special indexing. The options for this subtask are controlled be the `Printoptions` subtask. The parameters for the `Print` subtask are a list of table names.

4.4.3 Subtask Printoptions

This subtask allows the setting of the various print options such as labeling and column widths. The options set within this subtask remain in effect until they are turned off or reset. These options include:

`title` (*character string* *) Set the title for the header line on each page. The title string should be terminated with the '*' character.

`format` (*Fortran-style format*) Change the print format used. The default is `(1F10.5)`.

`width` (*number*) Change the maximum column width. If you change the `format` to print wider numbers, then you must also increase this width to fit.

[1] Remember that lists and tables are equivalent structures.

`relabel` (*listname*) `as` (*character string **) Change the label for specified `listname` to the `character string`.

`columns` *number* Set the number of columns displayed per page to *number*.

`pagelength`
lines Set the number of lines displayed per page to *lines*.

The following options apply only to `atom`, `residue`, `molecule` or `species` structures.

`nospecies`
Do not print species name.

`noresidue`
Do not print residue name.

`noatom` Do not print atom name.

4.4.4 Subtask Plot

This subtask plots $x-y$ graphs using the data contained in tables. `Plot` will draw a two dimensional graph using the tables supplied as parameters. If the first table parameter contains two real dimensions then the two dimensions will be plotted against each other. The first dimension is used for the y axis and the second is used for the x axis. Time lists created by the `starttrack` and `stoptrack` loops are best plotted this way. If there is only one dimension of real numbers in the first list then two or more lists are required. The first list will be used as the x axis and the remaining lists will be plotted on independent graphs as the y axis.

`Plot` Options available to this subtask are described in the `parseplot` section.

`model` If the MODEL option is given and the following list is of type `atoms` or `bondlist`, as part of the plot options you specify the REGIS output device, then you can view a simple 3 dimensional ball and stick model made up of the specified bonds. This task will grow when there is more need for it.

4.4.5 Subtask Write

This subtask stores Impact table structures in formatted disk files. These files may be reloaded in subsequent Impact jobs using the `read` subtask. Files created with `write` are transportable between different hardware platforms. In addition to the raw data in a table, files created with the `write` subtask will also contain all the information required to reconstruct the table data

structures used within Impact. Manual modifications of these files should be performed with care.

- `table`

  `write file` *fname* *'table_name'*

`quit`

4.4.6 Subtask Read

This subtask will load internal table structures from a formatted disk file into tables accessible within the Impact DICE environment. The `read` subtask assumes that input files are in the format produced by subtask `write`.

- `table`

  `read file` *fname* *'table_name'*

`quit`

4.4.7 Subtask Reset

This subtask allows the "updating" of built-in tables to reflect changes made by another Impact task. It also frees up memory if space available for lists starts to get small. The updating does not occur until the table is referenced again.

4.4.8 Subtasks Starttrack, Stoptrack and Traj

These related subtasks allow for the creation of "time tables," which are tables made by filling the results of a series of `put` subtasks over the changing data sets represented by one or more trajectory files. For an illustration, see Section C.3.5 [RDF (example)], page 296.

A *time table* is a table that contains a timestamp subfield in addition to any data fields, and is consequently a convenient structure to record the values of properties as they change during a series of trajectories. The `traj` subtask specifies the trajectory files to use. There are a number of options available to this subtask that are described in detail in the `trajectory` section. The subtask `starttrack` marks the start of a "loop". It also is where you can optionally specify which tables are to be stored as timelists. This optional syntax is:

- `define timelist` ... `from` *alist* `as timestep` ...

There can be N `timelists` specified between `define` and `from`. They represent the first to Nth elements of the list *alist* specified between the keywords `from` and `as`. You should not use `timelist` on command lines between `starttrack` and `stoptrack` since they will be automatically updated and created as you put values in the tracked list `table`. In the following example '*result.list*' is defined as a `timelist` and selected bond angles are appended to this list with a timestamp. The process is repeated at all trajectory frames

specified by the `trajectory` options. The following example is partly a meta example.

Example:

```
table
   trajectory  nfile number maxrec number nskip number unformatted deltat val -

     coor and veloc every num nobox traj fname file file1 file file2
   starttrack define 'result.list'  from 'my.angles' as timestep
     put residues:residue_name:atoms:atom_name: into 'my.atom'
     put 'anglelist_bang' with 'my.atom' into 'my.angles'
   stoptrack
   [ write file fname result.list | show result.list ]
quit
```

4.4.9 Subtask Restore

This subtask loads the contents of a table into a program array.

- `restore [ charge | velocity | xyz ] 'avg.coord'`

`xyz` the cartesian coordinates

`velocity` the velocity array

`charge` the charge array

Table *user_table* is the name of a table containing data to be copied to an internal array. The table must have the type corresponding to the array to be loaded.
In the following example the contents of the table 'avg.coord' is loaded into the cartesian coordinate common block and then these coordinates are written to a standard PDB format file.

```
xyz 'avg.coord'
create
print coord name protein file avgcoord.pdb brook
quit
```

The `restore` subtask could also be used to do free energy calculations:

```
put 0.0 into 'lambda'
put 'charge' with species:protein:residue:ala*:atoms:*: -
  into 'initcharge'
while 'lambda' le 1.0
put 'initcharge' * 'lambda' into 'newcharge'  !figure out new charges
restore charge 'newcharge'        !place newcharge into common block
...
<  dynamics run  >
...
```

```
put 'lambda' + 0.05 into 'lambda'
endwhile
```

At the end of a run like this 20 trajectory files would exist generated with 20 sets of charges. Note that the dynamics portion is done with a call statement to a file, which would need to contain a standard dynamics input. The use of such a call is indicated in the example below, in which the trajectories are analyzed to calculate the hydration energy (in task analysis) with the same variation in the charges. Note that `starttrack` and `stoptrack` would be needed to do the loop through each trajectory file. (Warning: the following would need considerable modification for any real system.)

```
put 0.0 into 'lambda'
put 'charge' with species:protein:residue:ala*:atoms:*: -
  into 'initcharge'
while 'lambda' le 1.0
put 'initcharge' * 'lambda' into 'newcharge' !figure out new charges
restore charge 'newcharge' ! places newcharge into common block
table
call trajinfo file trajinfo.inp
starttrack
quit
call analysis file hydrationanalysis.inp
put 'hydration' with species:protein:residue:ala*:atoms:*: -
  into 'e0'
put sum 'e0' into 'e0'
put 'hydr0' append 'e0' into 'hydr0'
reset 'hydration'
table
stoptrack
quit
put 'initcharge' * ('lambda'+0.05) -
  into 'newcharge'  !figure out new charges
restore charge 'newcharge' ! places newcharge into common block
table
call trajinfo file trajinfo.inp
starttrack
quit
call analysis file hydrationanalysis.inp
put 'hydration' with species:protein:residue:ala*:atoms:*: -
  into   'e1'
put sum 'e1' into 'e1'
put 'hydr1' append 'e1' into 'hydr1'
reset 'hydration'
```

```
table
stoptrack
quit
put 'lambda' + 0.05 into 'lambda'
endwhile
put 'hydr1' - 'hydr0' into 'diff' ! hydr1,hydr0 are hydration values
put sum 'diff' into 'answer'  ! sum the differences = hydration free energy
```

4.5 Binning Subtasks

The binning routines process previously created trajectory data for visualization using, e.g., the Data Visualizer. Currently, it is possible to view the solvent density, average dipole moments of the solvent, or the average solute-solvent interaction energy of the solvent molecules. Here we refer to a *box* and *bins*, where the box is a virtual box, and it overlays the simulated box of solvent molecules. The volume of the virtual box is gridded into a set of regularly spaced bins.

4.5.1 Subtask Binsolvent

`Binsolvent` determines the density of the solvent molecules in a simulation in each user defined bin within the solvent box. The output is in wave file format suitable for examination with the Data Visualizer.

```
table
   binsolvent
     grid [ center [ name spec [ resnumber resn [ atname atna ] ] ]
      [ rotate [ matrix ] | [ name spec [ resnumber resn -
      [ atn atomi atn atomj atn atomk ] ] ] ]
     init [ xl val yl val zl val] -
     [ xstep val ystep val zstep val ] -
     [ xori val yori val zori val ] -
     [ scale val ]
quit

table
   trajectory trajectory file info
quit
table echooff
   starttrack
quit
table
   binsolvent
     run
```

```
quit
table
   stoptrack
     closefiles
quit
table echoon
   binsolvent
     finish wave file fname
quit
```

where *trajectory file info* is as described in Section 4.2.1 [Input (mdanalysis)], page 166.

`grid` Determines the center of the binning grid, the default is the center of the box. The keyword `center` begins the definition of the box center, and can be defined by one or more of species, residue, or atom descriptors. For example only specifying `name` *spec* would translate the system so that the center of mass for the species would be at the box center (coordinate 0,0,0). For each frame the system is translated to that the chosen center of mass lies at the coordinate center.

`rotate` For each frame of the trajectory, rotate the system so that there is a common rotational reference. This should always be included in cases where the solute was not frozen during the original simulation and may be included for other cases. The default is to use atoms 1, 2 and 3 of the solute to define the rotation axes.

`rotate matrix`
Uses transformation matrices generated elsewhere to rotate the coordinates.

`initialize`
Perform various initialization prior to the application of `binsolvent run`; it should be the last `binsolvent` command called prior to using the run command. After the `init` function, the traj and starttrack commands should be used to read in the trajectory data

`xl, yl, zl`
Set the lengths of the x, y, and z edges for the solvent box.

`xori, yori, zori`
Set the origin of the binning grids/virtual box in the x, y and z dimensions.. These values are con-

ventionally -0.5 * boxlength (xl, yl and zl) to put point 0,0,0 in the center.

`xstep, ystep, zstep`
Set the grid stepsize.

`scale` Scale the resultant solvent density by this value.

`run` The `run` command performs the actual binning. The `table` function `stoptrack` is used after the `run` command.

`finish` `Finish` writes out the results of the binning process to *fname*. The keyword `wave` causes wave file format to be used. Otherwise, a stream of bin contents is written with the x index varying fastest.

4.5.2 Subtask Bindipole

`Bindipole` determines the average dipole moment of the solvent molecules from a molecular dynamics trajectory. Two types of output are available; one gives the vector dipoles, and the other gives the average dipole moment magnitude at each gridpoint.

Most commands are the same as for `binsolvent`, with the following exceptions: The `rotate matrix` option is not available. The `finish wave` option writes out the dipole moment magnitudes. The `finish vector` option outputs a file containing the averaged dipole moment vectors.

Example:

```
table
   bindipole
     finish [ vector ] file fname
quit
```

When more trajectory files are going to be opened than can be processed in a single Impact run, the output must be stored in the `vector` format so that averaging of the data can be performed later.[2]

4.5.3 Subtask Binenergy

`Binenergy` determines the average solute-solvent energy of the solvent molecules. The energy upon output is negated. This means that the most favorable energies will be positive and the least favorable will be negative in the output. This is done for better comparison with results from `binsolvent` Again, the commands are the same as for `binsolvent`, with the exception that the `rotate matrix` option is not available.

[2] A separate program for averaging across several files must be used in this case.

```
table
   binenergy
     finish wave file 'wavefile'
quit
```

5 Advanced Input Scripts

In this chapter, we will discuss some advanced features of Impact input scripts (DICE scripts). You will find it is very powerful after you spend some time with it. You can manipulate internal data lists; you can use `if else endif` statements inside the input file; you can specify a `while endwhile` do loop to control a simulation; you can even `call` a previously written script *subroutine* to perform a common task, etc.

5.1 Background

As you have probably noticed already, at its core Impact is a program for processing a series of commands in a control file, the *input file*. These basic commands comprise a set of powerful tools for modeling complex chemical structures; the three levels of commands are the *task*, *subtask* and the "program" levels. The last level is independent of which task or subtask is presently being used, and consists of a set of data structures and programming constructs. At the program level it is possible to write programs defining the execution of Impact, as well as to access and modify internal Impact data structures using *lists*. For example, counters can be created and incremented, tasks and subtasks can be executed inside of looping constructs, and the internal state of Impact can be examined or modified.

The task level communicates to the program that a group of complex operations will be performed. Each task is invoked by giving the task name alone on a line of the input file. For example, for the `dynamics` task, which integrates the equations of motion for a chemical system, the word `dynamics` appears alone on a line. This causes the program to branch into the portion that performs a molecular dynamics simulation. The word `quit` (alone on a line) ends the current task and returns the execution pathway to the main controller. At this point the subsequent task is performed.

Inside each task a series of subtasks are performed. Here details are given about the particular pathways to follow or parameters to use in the context of the current task. For example, in the task `setmodel` (which specifies the features of the energy model to be used in simulations) the subtask `setpotential` specifies the types and weights to be used in the energy function. The subtask `mixture` takes a solute molecule and places it in a box of solvent molecules.

At the lowest level, programming constructs and data structures are manipulated in a task/subtask independent way. When these programming constructs are used, the commands appear by themselves on a command line. For example, in using Impact's conditional construct, an `if` block, a line such as '`if 'a' eq 'b' dynamics endif`' would not work, however, the following multiple line command is acceptable:

```
if 'a' eq 'b'
```

```
    dynamics     ! do the task dynamics if 'a' and 'b' are equal
      < some dynamics operations >
    quit
  endif
```

The existence of a programming language inside of Impact greatly increases both its ease of use and the ability to express complex computational experiments that might otherwise be all but impossible to perform.

The data structures available in Impact are *scalars* and *lists*, which correspond to variables and constants in typical programming languages. Lists are perhaps most similar to arrays of records, and may contain one number, or thousands. An Impact list is like a two dimensional array in containing rows and columns; the number of rows is called the *size* and the number of columns is called the *dimension* of the list. An *element* of a list is, for example, the value at row 1 and column 1.[1] Generally the size of a list is flexible and will grow as needed, whereas the dimension is fixed and is determined by how the list was first created. Arithmetic operations on lists normally require that both operands be of the same dimension or that one be scalar. When used as a logical expression, an empty list will be the same as a false expression. Conversely, a list with any elements in it is a true expression.The elements of lists can be referenced in a number of ways.

5.1.1 Lists

For the user of Impact, the primary means to manipulate data is using the data structures referred to here as *lists* or *tables*.[2] The names of lists are **always** placed within single quotes when used, and these names have maximum lengths of 30 characters. All characters supported by the computer are allowed with the exceptions of single quotes and underscores. Some valid names are '*Validname*', '*themotherofalllists*" and '*abc123me&u*'. Note that underscores should not be used in list names since they are used to delimit columns of real numbers.

A list is a collection of related elements with a well defined structure, both in size and dimension. Some major types of list structures in Impact are atom, residue, molecule and species number; these types of structure are automatically recognized within Impact. Properties such as charge and surface area are frequently calculated in one of these types of list. Other types of list may also be used, for example lists to store properties with cartesian (x, y, z) components, or lists of position, force and velocity. Another type of list is a set of of statistics containing the three components sum, average and standard deviation.

[1] A list with size 1 and dimension 1 would be the same as a scalar variable found in many computer languages.

[2] Lists and tables are equivalent.

There are two broad catagories of lists, *user defined* and *internal*. Most properties are shared by these two types. However, several internal lists are tied to the internal system state. Internal lists are "peep holes" into the major Impact data structures. These lists are created the first time they are referenced as a copy of the current state of the related Impact data structure.[3] These lists are are structured according to the information contained within them, since Impact is able to create the structure of the list from the information in the chemical system currently being used. For example, the list `surfacearea` is structured by atom.

Both internal (built-in) and user defined lists only "come into existence" the first time they are specified. Because internal lists are only copies of the internal data structures used by Impact, they stay fixed after the initial copy is made, even if subsequent Impact tasks modify the corresponding internal data structures. These lists are only "refreshed" with current data when used the first time. To subsequently update the lists with new data the old copies are first erased using the `reset` command, after which any subsequent use of the list will cause it to be updated with the current Impact data. For later updating, the `reset` command must be used again. Many of these built-in lists are useful for storing information from tasks for later retrieval. This is particularly useful if dynamics is being run on the same system many times. Then the average of the averages of individual runs can be obtained.

While internal lists may be used before being assigned values, they will sometimes be undefined until certain subtasks are executed. For example, the `bondlist` has a component that is the actual bond energy, but this assumes that the parameters have been defined by using the `setmodel` task. The list `Current.kinetic` contains the current kinetic energy but this requires that `dynamics` has been run. Other internal lists requiring that a task or subtask be performed before they may be used are the lists for surface area (`surfacearea`) and the rms deviation (`rms.dev.atom`), where the analysis task must be run and the appropriate subtasks performed before the lists are properly defined. The creation of these lists is done automatically, and they may be used after the subtasks are run. The cartesian coordinate list (`cord`) can be used at any point after the task `create` is performed. In general, the contents of the list will vary depending on when the list is used. For example, the values of `cord` change after a dynamics run. Remember the caveat that the value of internal lists are set as soon as they are used, but if the values need to be updated the command `reset` must be used to clear the old contents of the list. The next use of the list name will then cause the values of the list to be updated.

[3] We emphasize that internal lists are user-accessible copies of the Impact data structures.

Global Impact built-in lists		
List name	List type	Impact tasks
surfacearea	atoms	analysis
hydration	atoms	
bondrr	residues	
torsionrr	residues	
14elerr	residues	
vdwerr	residues	
hb1012rr	residues	
totalrr	residues	
anglerr	residues	
14ljerr	residues	
noerr	residues	
eelrr	residues	
hbelrr	residues	
rmsfluctuations	atoms	mdanalysis
avg.temp	species	dynamics
avg.kinetic	species	
avg.bond	species	
avg.angle	species	
avg.torsion	species	
avg.nonbonded	species	
avg.lj612	species	
avg.coulomb	species	
avg.hbond	species	
avg.lj14	species	
avg.coulomb14	species	
avg.potenergy	species	
avg.totalenergy	species	
avg.translation	species	
avg.rotation	species	
avg.virial	species	
avg.tail	species	
current.kinetic	species	
current.translation	species	
current.rotation	species	
current.temp	species	

5.1.2 Internal Lists

The following tables show the internal ("built-in") lists that carry the current state of various Impact internal data structures.

Global `Impact` built-in lists (continued)		
List name	List type	`Impact` tasks
`potenergy`	species	`minimize, montecarlo,`
`current.bond`	species	or `dynamics`
`current.angle`	species	
`current.phi`	species	
`current.nonbonded`	species	
`current.lj612`	species	
`current.coulomb`	species	
`current.hbond`	species	
`current.lj14`	species	
`current.torsion`	species	
`current.buffer`	species	
`current.tail`	species	
`current.energy`	species	

Global `Impact` built-in lists with subfields				
List name	List type	Subfields (names)		
`atoms`	atoms			
`residues`	residues			
`molecule`	molecules			
`species`	species			
`force`	atoms	`x`	`y`	`z`
`velocity`	atoms	`x`	`y`	`z`
`box`	dimensions	`x`	`y`	`z`
`charge`	atoms			
`bondlist`	bonds	`bdis` (distance)	`enrg` (energy)	
`anglelist`	angles	`bang` (angle)	`enrg` (energy)	
`torsionlist`	torsions	`btors` (torsion)	`enrg` (energy)	
`cord`	atoms	`x`	`y`	`z`
`intcord`	atoms	`bnd` (bond)	`ang` (angle)	`phi` (torsion)

5.1.3 Subsets of Lists

It is often desirable to select an element, or sets of elements from lists. There are several ways to do this.

5.1.3.1 Underscore notation

Lists with multiple dimensions may be referenced by appending an appropriate suffix to the list name, where the format is '*listname_ref*'. For cartesian components the suffixes are `_x`, `_y` and `_z`, and for statistical components `_sum`, `_avg` and `_stdev`. For instance, the x component of the force list named `'myforce'` would be named `'myforce_x'`. A collection of other prefixes is:

```
_1    _2    _3
_bdis _enrg
_bang
_btors
_bnd  _ang  _phi
```

Another use of the underscore is to modify the order of printing or calculations. There are a number of field modifiers supported, and the order field modifiers appear will dictate the order they will appear in the resulting list.

`'cord_x_y_z'`	same as '`cord`'
`'cord_y_z_x'`	a 90 degree rotation
`'intcord_phi'`	only interested in the angle value
`'bondlist_enrg'`	only interested in bond energy
`'torsionlist_btors'`	only interested in torsion value

5.1.3.2 Lists as arrays

A range of list elements can be specified using square brackets. For instance, `'myforce_x[1:100]'` specifies the first 100 elements of the list of x component of force. A sublist may always be substituted for a list.

5.1.3.3 Colon notation

Subsets of lists can also be specified using *colon notation* and a number of list operations. Note that the properties defined using colon notation make up a *virtual* list when used with the *list selectors*, i.e., the `with` command. This is done by defining constraints (properties), each constraint building on the previous ones, until a collection of properties is specified that defines the structure of interest. With this structure you can then select a subset of elements from a list of interest.
In the following code fragment

`species:`*spec*`:molecule:`*mol*`:`

we specify a subset where the elements share the properties of (a) belonging to species *spec* and (b) belonging to molecule *mol*. In

`residue:`*res*`:atom:`*atom*`:`

the elements of the defined subset would belong to residue *res* and possess the atom name *atom*[1]. Any of these specifiers may be replaced by a range of names or numbers separated by a hyphen, or a group of comma-separated names or numbers. The wild card character '*' may be used to specify all names or numbers of a particular type, or it may also be used with any combination of symbols to create a name.
It is important to emphasize that the rightmost component of this structure specification determines the structural feature referenced. For instance,

[1] The specifiers *spec*, *res* or *mol* are names or numbers.

```
species:1:residue:1:atom:1
```

refers to atom number one in residue number 1; whereas

```
species:1:residue:1
```

refers to the entire first residue. Molecule is an optional specification. If the `species` or the `residue` specification is omitted then all species or all residues are implied. Here are some examples:

```
species:1                    ! species one
species:1:residue:1          ! the first residue in species one
species:Water                ! the species named Water
residue:1                    ! residue one
residue:1:atom:*             ! all atoms in residue one
residue:1-3,6:atom:*         ! all atoms in residues one through three and six
residue:1:atom:C*            ! all carbon atoms in residue one
residue:HYP*:atom:C*         ! all carbon atoms in all HYP residues
```

A constraint is one of the following:

- Any internal list that contains a valid structure (e.g., an atom, residue, molecule or species list).
- `species`:*ranges*:
- `molecules`:*ranges*:
- `residues`:*ranges*:
- `atoms`:*ranges*:

5.1.3.4 Hyphen notation

Ranges are a list of numbers separated by hyphen (inclusive) or commas *or* a list of strings with or without wild cards, the '`*`' character.

```
residues:1-4:atoms:CA,C,N:
molecules:1:atoms:1,3-5:
species:1:
residues:*:atoms:C*:
atoms:1-4:'myproperty'
```

Note that an attempt will be made to locate the specified structure throughout the whole system. For example, the query

```
atoms:1:
```

returns a list containing the first atom for *each residue* and not just the first atom of the entire system.

Once a structure is defined, a subset can be chosen where the elements share appropriate properties. In the following items the subsets are equivalent to lists. The list selector `with` is used here for selecting subsets from lists, and along with other selectors is described below.

- '`'surfacearea' with atoms:1-4:`' results in a subset of the list `surfacearea` corresponding to atoms 1 to 4.

- ‘’force_x_y’ with residues:1-3:atoms:*:’ results in a subset of the list force containing the x and y force components for all atoms in residues 1 to 3.
- ‘’rmsfluctuations’ with residues:4:atoms:h*:’ results in a subset of the list rmsfluctuations for all hydrogen atoms in residues 1 to 4.

Having selected the range of properties you wish to work with you can do operations on those properties. A large library of arithmetic and statistical functions is available.

5.1.4 List Creation

Lists are generally created using the command put; however, create has some uses that the other doesn’t. This latter command is specific to the task table (see Section 4.4 [Table (analysis)], page 175).

5.1.4.1 Put

The put statement is used to assign values to lists. In doing so the list is created if it didn’t already exist.

```
put 'expression' into 'list'
```

5.1.4.2 Create

Create a new list. This operation can only be performed inside of the task table (see Section 4.4 [Table (analysis)], page 175).

5.1.5 List Selection

As noted above, the properties describing subsets of lists are built up using several notations, and subsets of lists are actually constructed using list constructors like with; this and other list functions are described here. The resultant subsets are often placed in new lists, which is the convention followed in these examples.

5.1.5.1 With

The function with returns those elements in one list that are found in both lists. Atoms, molecules, residues, and species are recognized by these functions. In the following example those elements in the ’charge’ list belonging to atoms with names beginning with the letters ’CA’ are selected.

```
put 'charge' with atoms:CA*: into 'result'
```

5.1.5.2 Withonly

The withonly function extracts those elements in the list whose atom, molecule, residue or species specification match the entire target specifi-

cation. In the following example, only those bonds containing **both** CA* and N* atoms are extracted. In contrast the selector `with` returns all bonds with CA or N atoms.

```
put 'bondlist' withonly atoms:CA*,N*: into 'result'
```

5.1.5.3 Without

The `without` function returns those elements in the first list that do not have relations with the second list. This example extracts those elements from the torsional internal coordinate list that are not hydrogen atoms.

```
put 'intcord_phi' without atoms:h*: into 'result'
```

5.1.5.4 By

The `by` function returns a list that is the result of applying the previous function over a long list split up by its structures. `By` requires two lists. One of these is called the limit and must be of type residue, molecule or species, and the other is called the *range* and must be of type atom, residue or molecule. The result is a list the same length as the limit, with each element storing the result of applying the previous function over the range split up along the structures of the limit. The functions you can apply `by` to include: `abs`, `int`, `avg`, `stat`, `sum`, `sum2`, `ln`, `sin`, `cos`, `tab`, `asin`, `acos`, and `atan`. The following example results in a list of type residue with each element storing the sum of the atom charges for each residue. (In most cases this would be a of list of zeros, ones and minus ones.)

```
put sum 'charge' by 'residue' into 'result'
```

5.2 Operations on Data

A range of functions and list-selectors are available, including the standard arithmetic expressions and a set of functions defined solely for lists. A *list expression* is a list or any arithmetic or functional expression that results in a list, and a list-expression may always be substituted for a list. The arithmetic operators include exponentiation (`^`), multiplication (`*`), division (`/`), addition (`+`), subtraction (binary `-`) and negation (unary `-`). These may be applied to constants, such as '`2 * 2`', or used as *list operators*. Operations may be performed between lists with common structures, or between lists and scalars.

When operations occur between lists of different dimensions, the result of the operation inherits the dimensionality of the list of higher dimension. Consider the following examples in which '*myforces*' is a list of atomic forces having an atomic cartesian (x, y, z) structure, '*jscal*' is a user-defined list having a simple atomic structure, and '*const*' is a scalar sonstant.

'*myforces*`_x' * '`*jscal*'

multiplies the corresponding elements of the x component of '*myforces*' and '*jscal*'.

5.2.1 General Operations

Arithmetic functions are applied to a list in one of three ways:

1. If one of the operators is a single element, the operation is done with the value of that element against all the values in the other list. (That means that you can multiply an entire list by a single constant.)
2. Some functions take only a single list and return a few elements of information about that list, such as the average value of the list, or its four (4) greatest values.
3. If you are applying a function between two lists and both lists have size greater than 1, that function will be applied to each element in the two lists that correspond to each other. This means you can add the values of two lists in an element by element manner.

```
1 + 'mydata'                    ! every element gains 1
'mydata' + 'mydata'             ! <--- these are
2 * 'mydata'                    !      the same
'mydata' pow 0.33333            !  cube root
7 lowest 'mydata'               ! sorted lowest 7 elements
avg 'mydata'                    ! the list average put in a new 1 element list
(sum 'mydata')/(length 'mydata') ! silly way to avg
('newdata'+'olddata')/2         ! result is a new list consisting of the
                                !  average values of each of the list elements
```

```
'myforces_x' * 'const'
```

multiplies all the x components of *'myforces'* by the value of *'const'*. The command

```
'myforces' + 2.0
```

adds the value of 2.0 to all of the components (x, y, z) of *'myforces'*.

General Operators			
Operator	Function	Parameters	Units
`+`	Addition	2	
`-`	Subtraction	2	
`*`	Multiplication	2	
`/`	Division	2	
`abs`	Absolute value	1	
`acos`	Arc Cosine	1	radian
`add`	Addition	2	
`asin`	Arc Sine	1	radian
`atan`	Arc Tangent	1	radian
`avg`	Average	1	
`avgb`	Special case of `by` function	2	
`by`	Apply a 1 parameter function over a list of values (e.g. `sum 'charge' by 'residues'`)		
`cos`	Cosine	1	radian
`distance`	Distance Function	2	cord units
`div`	Division	2	
`grdist`	Greatest Distance	2	atoms units
`greatest`	N Maximum values e.g., `3 greatest 'bondlist_bdis'`	2	
`index`	Extracts an element from a list e.g. `index 10 'charge'` gets the 10th value from the charge list)	2	
`int`	Truncation	1	
`length`	Size of list	1	
`lowest`	N Minimum values	2	
`ln`	Natural Log	1	
`^`	Exponentiation	2	
`exp`	Exponentiation (base e)	1	
`lstdist`	Least Distance	2	atoms units
`alldist`	All distances	2	atoms units
`hist`	Histogram	2	
`max`	Maximum value	1	
`min`	Minumum value	1	
`mul`	Multiplication	2	
`pow`	Power function (base 10)	1	
`rand`	Random number	1	
`runavg`	Running Average	1	

General Operators			
Operator	Function	Parameters	Units
`sin`	Sine function	1	radian
`sizeof`	Size of list	1	
`sqrt`	Square root	1	
`sqr`	Square	1	
`stat`	Sum, Average, Standard Deviation	1	result is dimension 3
`std`	Standard deviation	1	
`sub`	Subtraction	2	
`sum`	Add all columns	1	
`sum2`	Add and square columns	1	
`sumby`	Special case of `by`		
`tan`	Tangent function	1	radian

Relational Operators	
Name of function	Example of usage
`and`	`if ('timer' gt 1) and (atoms:ca:)`
`eq`	`131 eq 23`
`ge`	`'charge' ge 0.2`
`gt`	`'bondlist_bdis' gt 1.2`
`le`	`'bondlist_bdis' le 1.1`
`lt`	`'anglelist_bang' lt 45`
`not`	`if not ( 'timer' gt 50 )`
`or`	`while ( 'counter' lt 100) or ( sum 'list' lt 1 )`
`xor`	`avg ( species:*:atoms:c*:)  xor avg ( species:*:ca:)`

5.2.2 Relational Operators

Relational operators may be used to perform list comparisons, and include `lt`, `le`, `eq`, `gt`, and `ge`. For example, the following relational expression could be used to select the forces greater than 0.05:

```
('myforces_x'^2 + 'myforces_y'^2 + 'myforces_z'^2)^0.5 gt 0.05
```

The boolean operators `and`, `or` and `not` may be used to combine relational expressions; in particular, a "not-equal" operation can be performed by using `not` to negate an `eq` comparison.

In addition to the standard mathematical operators, Impact provides many higher level operators that perform selection operations on lists. For instance, the `with` operator allows a constraint to be applied to a list. In this example, `with` is employed to restrict the list of surface area for each atom to those cases in which the charge on each atom in list `'qbyatom'` is greater than 0.2:

```
put 'surfbyatom' with ('qbyatom' gt 0.2)  into 'result'
```

Character and String Operators		
Operator	Function	Parameters
`char`	Integer to char conversion	1
`concat`	Append two strings	1

5.2.3 List Operators

Here the remaining list operations are fully described. These are really context-independent subtasks and are not expressions.

5.2.3.1 Restore

`Restore` copies the contents of a list to an internal list, from where it will be copied to one of the the internal data structures used in Impact (e.g., a common block). One such internal data structure is `charg`, another is `xyz`. For example, if some operations have been performed on a list of coordinates it may be desirable to have one of the standard tasks operate on these new coordinates. Note the required use of the square brackets as delimiters!

```
put 'cord' + [ 0.10 0.10 0.10 ] into 'cord' ! translate coordinate list
restore xyz 'cord'      ! put it back into the actual cartesian coordinates
dynamics                ! now run dynamics
```

5.2.3.2 Rand

The `rand` function returns a single random number in the range 0.0 to the first element of its parameter. A negative parameter resets the seed number.

5.2.3.3 Smooth

The `smooth` function returns a list that has less noisy data points. *Smooth* breaks up the input list into a series of short ranges and preserves for the final output those elements that are the mean value of the short ranges. The size of the range is determined by the first element of the first parameter, which should be an odd number such as 3, 5 or 7. Very large ranges will result in serious loss of information.

5.2.3.4 Histogram

The `hist` (histogram) function does a count frequency on a list (first parameter) using parameters in a second list. The first list can be any list with no more than 3 real columns of data. The second list must contain the minimum value of the histogram, the number of intervals and the width of each interval. This information can be stored in a list as in [0.0 100 0.25] or as a list of 3 elements each with 1 real field, e.g., ‘ `0.0 append 100 append 0.25`’. The result of this function is a list with the same number of real

columns as the first argument containing the count of values in each interval plus an additional column containing the values of each interval (e.g., the above parameters would give 0.0, 0.25, 0.50, etc).

5.2.3.5 Distance

The `distance` function returns the distance between two coordinate sets. Coordinates are in x y z format. The coordinates for the current system are stored in the built-in parameter list named `'cord'`.

The `grdist` and `lstdist` functions return the greatest or least distance from every atom in the first parameter from every atom in the second parameter. The function `alldist` returns a list of all distances between the two input lists. This function should be used carefully since it creates lists of the size of $n \times m$ where n and m are the size of the atom lists used as parameters. The result is a bond list.

5.2.3.6 Plotting lists

The subtask `plot` is defined inside of the `table` task, and is the general means for plotting lists (see Section B.1 [Plot (plot)], page 231). Many other tasks also have their own `plot` subtasks as well, however, and these generally use the same mechanism. Thus, `plot` is almost a task-independent subtask.

5.3 Advanced Scripts

Using the tools available in Impact, you can program simple tasks that allow one to:

- analyze data as it is being generated;
- automate simulations, look at results, modify input files and relieve resubmission drudgery;
- provide an easier method to plot and study Impact compatible data;
- analyze the result of past Impact runs stored in trajectory files;
- provide a mini programming language to allow simple algorithms not yet implemented in Impact to be tested with access to the Impact data bases for run time analysis.

A good example is seen in Section C.3.5 [RDF (example)], page 296.

5.3.1 Flow Control

Essential tools needed to control the flow of a program are provided.

5.3.1.1 While

The `while` statement is used to conditionally execute the contents of its body, repeating until the condition is false. While you can nest these loops, it is *very* important that you never use the `goto` statement to jump inside of one. The format of the `while` statement is

```
while expression
  body of while loop
endwhile
```

5.3.1.2 If/else/endif

In an `if` expression, the first expression following `if` is tested for its truth value. If true the *body* is executed. If an `else` is present then the *optional code* following `else` is executed when *expression* is false.

```
if expression
   body
else
   optional code
endif
```

`If` statements may also be nested, with one `endif` for every `if`. As in the case of the `while` statement it is illegal to jump into an `if` block using a `goto`.

5.3.1.3 Goto

`Goto` is provided but not recommend. The format of the `goto` statement is

```
:label                  ! note the colon
some code
goto label              ! loop to label
```

As noted, a `goto` may not cause a jump into the body of an `if` block or of a `while` block.[1] Use of a `goto` statement to jump out of an `if` or `while` block can cause stack overflows if done repeatedly.[2] A `goto` jump from within one `if` or `while` block into another `if` or `while` block will, of course, be fatal.

5.3.2 Subroutines

Call a subroutine and return. `Call` passes its optional parameters by the method of "pass by name"; this is a somewhat obscure method of passing parameters. "Pass by name" from the user's viewpoint is equivalent to "pass by reference". This means that any change in the value of the parameters within a subroutine will be passed back to the calling routine. Care must be

[1] A block is all tasks up to the `endwhile` or `endif`.

[2] In a purely theoretical sense this is the only legitimate use for `goto`, and should properly be called break or exit.

taken to be sure that the main procedure does not extend into a subroutine. You should always follow the main procedure by the keyword `end`.

```
call alpha(100 'a' 'result')   ! call the subroutine
some more code
:alpha('a' 'b' 'c')            ! bind a, b, c to 100, 'a',, and 'result'
  definition body         ! perform calculations
put 'somevalue' into 'c'       ! return the result in variable 'result'
return
```

You may also append a file name after a `call`, this will cause the program to execute that subroutine within that file. Note that except for this special case all subroutines are searched for from the top of the current program in a first found, first executed manner.

```
call label [ parameters ] file fname
```

5.3.3 Spawn

`Spawn` starts a shell process at the operating system level and waits for the result.

```
spawn shell command UNIX shell command
spawn shell file executable file's name
```

5.3.4 Lists as Parameters

Numeric lists can be placed anywhere a number normally can be specified; if an operation requires a scalar value then the first element from the list's numeric field is used. Short character lists can also be used to hold filenames, which is especially useful when many files are being created and unique names are needed. Though we are getting ahead of ourselves by discussing specific tasks in the following example,[3] it does illustrate the use of different list operations and types of lists. Here we loop over the `run` subtask in `dynamics`[4]. While it would often only be desired to save the final state in a restart file, saving intermediate states assures that intermediate work has been saved if the job is terminated for any reason. A series of trajectory files might be saved in the same way.

`'i'` is a list that is used as if it were an integer variable.

`'filename'`
: is a list of characters that is modified in each stage of the dynamics run. Thus, unique trajectory files may be written for each phase.

[3] The example uses meta-variables that are explained in Chapter 2 [Setup System], page 17.
[4] The task `dynamics` is described in Section 3.2 [Dynamics], page 77

`$protein$ and $ps$`
: are string constants. Note the use of the dollar sign to delimit string constants.

5.4 Examples

Here we provide a few examples to show how to use the advanced Impact input scripts for various simulations.

The input files illustrate the calculation of quantities from a molecular dynamics simulation of a protein in solution, where trajectory information has been saved as a series of restart and PDB files written at 1 psec intervals and named accordingly, eg. '`gpla_1.pdb`', '`gpla_2.pdb`', etc.

5.4.1 Backbone and Sidechain Torsion Angles

This example demonstrates the calculation of backbone phi and psi angles within the protein (sidechain torsions can be obtained using the commented block of commands). The Impact input file is straightforward. By using the *phi* field of the built-in `intcord` list and limiting the retrieved entries to only those defining the tree-structure dihedrals for the backbone carbon and nitrogen atoms, the backbone phi and psi angles are obtained. The output file contains a table of backbone phi and psi angles in the format:

```
     SPECIES      MOL   RESIDUE    ATOM  PHILIST
-------------------------------------------------------
GPLA                1 LYSB1        N     243.91507
                                   C      36.37835
                       GLN2        N      84.31257
                                   C     299.98637
                       LEU3        N     105.24259
                                   C     295.60936
                       THR4        N     138.06053
                                   C     281.44445
                       LYS5        N     105.51490
                                   C     325.68637
                       CYX6        N     302.77196
                                   C     300.26761
                       ALA7        N     326.31558
                                   C     283.14148
```

For a residue i, the value listed under N is psi(i-1) and the value listed under C is phi(i).

The Impact input file:

```
WRITE file torsion.out -
      title calculate torsion angles of a protein*
CREATE
        build newresidue lysb file lysb glne file glne
        build primary name gpla type protein -
                lysb gln leu thr lys cyx ala leu ser hid glu leu asn -
                asp ile ala gly tyr arg asp ile thr leu pro glu trp -
                leu cyx ile ile phe hid ile ser gly tyr asp thr gln -
                ala ile val lys asn ser asp hid lys glu tyr gly leu -
                phe gln ile asn asp lys asp phe cyx glu ser ser thr -
                thr val gln ser arg asn ile cyx asp ile ser cyx asp -
                lys leu leu asp asp asp ile thr asp asp ile met cyx -
                val lys lys ile leu asp ile lys gly ile asp tyr trp -
                leu ala hid lys pro leu cyx ser asp lys leu glu gln -
                trp tyr cyx glu ala glne end
        build cross name gpla resn 6 atna sg resn 120 atna sg -
                name gpla resn 28 atna sg resn 111 atna sg -
                name gpla resn 73 atna sg resn  91 atna sg -
                name gpla resn 61 atna sg resn  77 atna sg
        read coordinates name gpla file gpla_880.pdb
QUIT

SETMODEL
        setpotential
                mmechanics
        quit
        read parm file paramstd.dat noprint
        energy parm cutoff 8.0 listupdate 10 diel 1.0 nodistance print 1
        energy constraint bond lonepair
QUIT

!  Backbone torsion angles
put 'intcord_phi' with only atoms:N,C: into 'philist'
show 'philist'

!  Sidechain torsion angles
!put 'torsionlist_btors' without atoms:n,o,c,h*,lp*: into 'tlist'
!show 'tlist'

end
```

5.4.2 Hydrogen Bonding

This example demonstrates the calculation of the number of intramolecular (protein-protein) hydrogen bonds for structures collected at 10 psec intervals using a distance cutoff of 2.5 Å and an angle cutoff of 120 degrees. The hydrogen bonds are decomposed into those occuring within the helices and sheet, between helix or sheet residues and neighboring residues, and by domains of the protein. This example demonstrates the use of the `concat` command operating on lists to build the restart file names and the subsequent reading of the files using the dynamics task. The `plot` subtask of task `table` is used to write the times in psec and number of hydrogen bonds to the output file. The subroutine named *analhb*, stored in an external file, is called to decompose the '*hbond*' list generated by the analysis task into the hydrogen bond types of interest. Taking the A-helix as an example, limiting the hydrogen bond list `withonly` the residue range of the A-helix yields hydrogen bonds for which both the donor and the receptor are from that helix. Limiting the hydrogen bond list using `with`, the residue range yields hydrogen bonds for which at least one of the hydrogen bonded residues is part of the helix. That is, the new list contains hydrogen bonds within the A-helix and between the A-helix and neighboring residues. Using `without` to remove intra-helix hydrogen bonds then gives the list of hydrogen bonds between the A-helix and neghboring residues. Using `sizeof` counts the number of entries in each list and thus yields the number of hydrogen bonds of a given type.

```
write file hbond.out -
title calculation of protein intramolecular hydrogen bonding *
create
        build newres lysb file lysb glne file glne
        build primary name alc type prot -
                lysb gln leu thr lys cyx ala leu ser hid glu leu asn -
                asp ile ala gly tyr arg asp ile thr leu pro glu trp -
                leu cyx ile ile phe hid ile ser gly tyr asp thr gln -
                ala ile val lys asn ser asp hid lys glu tyr gly leu -
                phe gln ile asn asp lys asp phe cyx glu ser ser thr -
                thr val gln ser arg asn ile cyx asp ile ser cyx asp -
                lys leu leu asp asp asp ile thr asp asp ile met cyx -
                val lys lys ile leu asp ile lys gly ile asp tyr trp -
                leu ala hid lys pro leu cyx ser asp lys leu glu gln -
                trp tyr cyx glu ala glne end
        build cross name alc resn 6 atna sg resn 120 atna sg -
                        name alc resn 28 atna sg resn 111 atna sg -
                        name alc resn 73 atna sg resn  91 atna sg -
                        name alc resn 61 atna sg resn  77 atna sg
quit
```

```
setmodel
  read parm file paramstd.dat noprint
  enrg parm cutoff 78.0 diel 1.0 nodist listupdate 10
  setp
   mmec
  quit
quit

put 1 into 'counter'
while 'counter' le 880

!  Build filename from counter value
put ($gpla_$ concat (concat (char 'counter') $.rst$ )) into 'rstfile'
!  Use dynamics task to read restart file
Dynamics
   read restart coordinates box external real4 file 'rstfile'
Quit

analysis
        ener hbond analyze hbond hbcut 2.5 hbangcut 120.0 echooff
quit
call analhb file analhb_new_cor.inp                 ! call a subroutine

put 'time' append 'counter' into 'time'             ! collect data
put 'totalhbs' append 'totalhb' into 'totalhbs'     ! at each psec
put 'has' append 'ha' into 'has'
put 'hbhs' append 'hb' into 'hbhs'
put 'hcs' append 'hc' into 'hcs'
put 'ss' append 's' into 'ss'
put 'ads' append 'ad' into 'ads'
put 'bds' append 'bd' into 'bds'
put 'interdoms' append 'interdom' into 'interdoms'
put 'ias' append 'ia' into 'ias'
put 'ibs' append 'ib' into 'ibs'
put 'ics' append 'ic' into 'ics'
put 'iss' append 'is' into 'iss'

put 'counter' + 1 into 'counter'
endwhile

table
        plot 'time' 'totalhbs' tabular file totalhb.dat
```

```
        plot 'time' 'has' tabular file ahelix.dat
        plot 'time' 'hbhs' tabular file bhelix.dat
        plot 'time' 'hcs' tabular file chelix.dat
        plot 'time' 'ss' tabular file sheet.dat
        plot 'time' 'ads' tabular file alpha.dat
        plot 'time' 'bds' tabular file beta.dat
        plot 'time' 'interdoms' tabular file interdom.dat
        plot 'time' 'ias' tabular file intera.dat
        plot 'time' 'ibs' tabular file interb.dat
        plot 'time' 'ics' tabular file interc.dat
        plot 'time' 'iss' tabular file inters.dat
quit

end
```

The subroutine called by Impact (read from file *analhb_new_cor.inp*:

```
:analhb

 put 'hbond' with atoms:o,oe*,ne*,og*,od*,oh: into 'hbs'
 put sizeof 'hbs' into 'totalhb'

 !  Select hydrogen bonds within and between helices, sheets, and domains
 !  A-Helix
 put 'hbond' withonly residues:5-11:atoms:*: into 'helixa'
 put sizeof 'helixa' into 'ha'
 put 'hbond' with residues:5-11:atoms:*: into 'allhelixa'
 put 'allhelixa' without 'helixa' into 'intera'
 put sizeof 'intera' into 'ia'
 !  B-Helix
 put 'hbond' withonly residues:25-34:atoms:*: into 'helixb'
 put sizeof 'helixb' into 'hb'
 put 'hbond' with residues:25-34:atoms:*: into 'allhelixb'
 put 'allhelixb' without 'helixb' into 'interb'
 put sizeof 'interb' into 'ib'
 !  C-Helix
 put 'hbond' withonly residues:85-99:atoms:*: into 'helixc'
 put sizeof 'helixc' into 'hc'
 put 'hbond' with residues:85-99:atoms:*: into 'allhelixc'
 put 'allhelixc' without 'helixc' into 'interc'
 put sizeof 'interc' into 'ic'
 !  Sheet
 put 'hbond' withonly residues:40-44,47-50:atoms:*: into 'sheet'
 put sizeof 'sheet' into 's'
```

```
put 'hbond' with residues:40-44,47-50:atoms:*: into 'allsheet'
put 'allsheet' without 'sheet' into 'inters'
put sizeof 'inters' into 'is'
!  By domain
put 'hbond' withonly residues:1-37,85-123:atoms:*: into 'alpha'
put sizeof 'alpha' into 'ad'
put 'hbond' withonly residues:38-84:atoms:*: into 'beta'
put sizeof 'beta' into 'bd'
put ('totalhb' - 'ad') - 'bd' into 'interdom'

!  The identity of the hydrogen bonding atoms can be obtained
!  by printing out the lists, eg.
!show 'helixa'
!show 'intera'
!show 'helixb'
!show 'interb'
return
```

5.4.3 Surface Area and Accessibility

This example demonstrates the calculation of the surface area of a protein and of the accessibility per residue relative to that expected for an extended chain. A `while` loop and a '`counter`' list are used for flow control. This example also demonstrates the use of the `concat` command operating on lists to build the restart file names and the subsequent reading of the files using the `dynamics` task. Surface area is calculated using the `surface` subtask of task `analysis`. Lists are used to obtain the surface area per atom and per residue and for the protein as a whole averaged over the simulation.

Subroutine `percent` from file '`percentacc.inp`' is called from the main input file. This subroutine contains surface area values for residues in an extended chain as calculated from Gly-X-Gly tripeptides (using a 1.4 Å probe radius). Accessibility is defined as the surface area of a residue in a protein divided by its surface area in an extended chain. Accessibilities are calculated for each residue and collected in list '*pcacc*'. In the main input file, the accessibilities are then collected by residue type. The accessibilities for a particular type are summed using the `sum` operation on the list and then counted using the `sizeof` operation to calculate the average accessibility per type.

```
write file sa_acc.out -
title calculation of protein surface area and accessibility *
create
        build newres lysb file lysb glne file glne
        build primary name alc type prot -
```

```
                lysb gln leu thr lys cyx ala leu ser hid glu leu asn -
                asp ile ala gly tyr arg asp ile thr leu pro glu trp -
                leu cyx ile ile phe hid ile ser gly tyr asp thr gln -
                ala ile val lys asn ser asp hid lys glu tyr gly leu -
                phe gln ile asn asp lys asp phe cyx glu ser ser thr -
                thr val gln ser arg asn ile cyx asp ile ser cyx asp -
                lys leu leu asp asp asp ile thr asp asp ile met cyx -
                val lys lys ile leu asp ile lys gly ile asp tyr trp -
                leu ala hid lys pro leu cyx ser asp lys leu glu gln -
                trp tyr cyx glu ala glne end
        build cross name alc resn 6 atna sg resn 120 atna sg -
              name alc resn 28 atna sg resn 111 atna sg -
              name alc resn 73 atna sg resn  91 atna sg -
              name alc resn 61 atna sg resn  77 atna sg
        build solvent name solvent1 type spc nmol 5721 h2o
quit
put 0 into 'count'
put 0 into 'sumsurf'

put 1 into 'counter'
while 'counter' le 880

!  Build filename from counter value
put ($gpla_$ concat (concat (char 'counter') $.rst$ )) into 'rstfile'
!  Use dynamics task to read restart file
Dynamics
   read restart coordinates box external real4 file 'rstfile'
Quit

!  Calculate Surface Area
        reset 'surfacearea'
        analysis
            surf name alc noprint type noh
        quit
        put 'surfacearea' with species:1: into 'surfacearea'
        put 'count' + 1 into 'count'
        put 'surfacearea' + 'sumsurf' into 'sumsurf'
        put sum 'sumsurf' by 'residues' into 'surfres'
        put 'surfres' / 'count' into 'surfres'
put 'counter' + 1 into 'counter'
endwhile

show 'count'
```

```
!! Print average surface area values per atom
put 'sumsurf' / 'count' into 'sumsurf'
show 'sumsurf'

!! Print average surface area values per residue
show 'surfres'

!! Print average total surface area
put sum 'sumsurf' into 'avgsurf'
show 'avgsurf'

!! Calculate accessibility
        call percent file percentacc.inp           ! call a subroutine

!! Collect accessibility by Residue Types

! hydrophobic residues
put 'pcacc' with residues:ala*,val*,ile*,leu*,phe*,pro*,met*: -
        into 'pcacchyd'
show 'pcacchyd'
put sum 'pcacchyd' into 'sumhyd'
show 'sumhyd'
put sizeof 'pcacchyd' into 'temph'
put 'sumhyd' / 'temph' into 'acchyd'
show 'acchyd'

! polar residues (without glycine)
put 'pcacc' with residues:ser*,thr*,cy*,tyr*,asn*,gln*,hi*,trp*: -
        into 'pcaccpol'
put 'pcaccpol' without residues:glne123: into 'pcaccpol'
show 'pcaccpol'
put sum 'pcaccpol' into 'sumpol'
show 'sumpol'
put sizeof 'pcaccpol' into 'tempo'
put 'sumpol' / 'tempo' into 'accpol'
show 'accpol'

! polar residues (with glycine)
put 'pcacc' with residues:ser*,thr*,cy*,tyr*,asn*,gln*,hi*,trp*,gly*: -
        into 'pcaccpolg'
put 'pcaccpolg' without residues:glne123: into 'pcaccpolg'
show 'pcaccpolg'
put sum 'pcaccpolg' into 'sumpolg'
```

```
show 'sumpolg'
put sizeof 'pcaccpolg' into 'tempy'
put 'sumpolg' / 'tempy' into 'accpolg'
show 'accpolg'

! negative residues
put 'pcacc' with residues:asp*,glu*,glne123: -
        into 'pcaccneg'
show 'pcaccneg'
put sum 'pcaccneg' into 'sumneg'
show 'sumneg'
put sizeof 'pcaccneg' into 'tempn'
put 'sumneg' / 'tempn' into 'accneg'
show 'accneg'

! positive residues
put 'pcacc' with residues:lys*,arg*: -
        into 'pcaccpos'
show 'pcaccpos'
put sum 'pcaccpos' into 'sumpos'
show 'sumpos'
put sizeof 'pcaccpos' into 'tempp'
put 'sumpos' / 'tempp' into 'accpos'
show 'accpos'

! glycines
put 'pcacc' with residues:gly*: -
        into 'pcaccgly'
show 'pcaccgly'
put sum 'pcaccgly' into 'sumgly'
show 'sumgly'
put sizeof 'pcaccgly' into 'tempg'
put 'sumgly' / 'tempg' into 'accgly'
show 'accgly'

!! percent solvent access. = acc*  X 100

end
```

The subroutine called by Impact:

```
:percent
!  Subroutine contains surface area values for residues in
!  an extended chain as calculated from Gly-X-Gly tripeptides
```

```
!   accessibility = surface area(X) in protein / surface area(X) in Gly-X-Gly
        put 'surfres' with species:1:residues:ala*: into 'surfala'
        put 'surfala' / 124.51 into 'surfala'
        put 'surfres' with species:1:residues:arg*: into 'surfarg'
        put 'surfarg' / 267.80 into 'surfarg'
        put 'surfres' with species:1:residues:asn*: into 'surfasn'
        put 'surfasn' / 170.98 into 'surfasn'
        put 'surfres' with species:1:residues:asp*: into 'surfasp'
        put 'surfasp' / 157.45 into 'surfasp'
        put 'surfres' with species:1:residues:cyx*: into 'surfcyx'
        put 'surfcyx' / 154.57 into 'surfcyx'
        put 'surfres' with species:1:residues:gln*: into 'surfgln'
        put 'surfgln' / 202.64 into 'surfgln'
        put 'surfres' with species:1:residues:glu*: into 'surfglu'
        put 'surfglu' / 191.12 into 'surfglu'
        put 'surfres' with species:1:residues:gly*: into 'surfgly'
        put 'surfgly' / 91.17 into 'surfgly'
        put 'surfres' with species:1:residues:hi*: into 'surfhis'
        put 'surfhis' / 205.33 into 'surfhis'
        put 'surfres' with species:1:residues:ile*: into 'surfile'
        put 'surfile' / 192.73 into 'surfile'
        put 'surfres' with species:1:residues:leu*: into 'surfleu'
        put 'surfleu' / 196.76 into 'surfleu'
        put 'surfres' with species:1:residues:lys*: into 'surflys'
        put 'surflys' / 236.21 into 'surflys'
        put 'surfres' with species:1:residues:met*: into 'surfmet'
        put 'surfmet' / 211.14 into 'surfmet'
        put 'surfres' with species:1:residues:phe*: into 'surfphe'
        put 'surfphe' / 231.92 into 'surfphe'
        put 'surfres' with species:1:residues:pro*: into 'surfpro'
        put 'surfpro' / 158.96 into 'surfpro'
        put 'surfres' with species:1:residues:ser*: into 'surfser'
        put 'surfser' / 138.10 into 'surfser'
        put 'surfres' with species:1:residues:thr*: into 'surfthr'
        put 'surfthr' / 166.49 into 'surfthr'
        put 'surfres' with species:1:residues:trp*: into 'surftrp'
        put 'surftrp' / 270.13 into 'surftrp'
        put 'surfres' with species:1:residues:tyr*: into 'surftyr'
        put 'surftyr' / 244.87 into 'surftyr'
        put 'surfres' with species:1:residues:val*: into 'surfval'
        put 'surfval' / 167.57 into 'surfval'
!!
put 'surfala' into 'pcacc'
```

```
put 'pcacc' append 'surfarg' into 'pcacc'
put 'pcacc' append 'surfasn' into 'pcacc'
put 'pcacc' append 'surfasp' into 'pcacc'
put 'pcacc' append 'surfcyx' into 'pcacc'
put 'pcacc' append 'surfgln' into 'pcacc'       ! collect accessibility
put 'pcacc' append 'surfglu' into 'pcacc'       ! values into table
put 'pcacc' append 'surfgly' into 'pcacc'       ! 'pcacc'
put 'pcacc' append 'surfhis' into 'pcacc'
put 'pcacc' append 'surfile' into 'pcacc'
put 'pcacc' append 'surfleu' into 'pcacc'
put 'pcacc' append 'surflys' into 'pcacc'
put 'pcacc' append 'surfmet' into 'pcacc'
put 'pcacc' append 'surfphe' into 'pcacc'
put 'pcacc' append 'surfpro' into 'pcacc'
put 'pcacc' append 'surfser' into 'pcacc'
put 'pcacc' append 'surfthr' into 'pcacc'
put 'pcacc' append 'surftrp' into 'pcacc'
put 'pcacc' append 'surftyr' into 'pcacc'
put 'pcacc' append 'surfval' into 'pcacc'
return
```

5.4.4 Radius of Gyration

This example demonstrates the calculation of the radius of gyration, a measure of the overall size the protein. This example uses the `concat` command operating on lists to build the PDB file names and subsequently reads the previously written files using the `create` task. The `plot` subtask of task `table` is used to write the simulation times in psec and the values calculated for the radius of gyration to a file.

```
write file rg.out -
title calculation of protein radius of gyration *
create
        build newres lysb file lysb glne file glne
        build primary name alc type prot -
                lysb gln leu thr lys cyx ala leu ser hid glu leu asn -
                asp ile ala gly tyr arg asp ile thr leu pro glu trp -
                leu cyx ile ile phe hid ile ser gly tyr asp thr gln -
                ala ile val lys asn ser asp hid lys glu tyr gly leu -
                phe gln ile asn asp lys asp phe cyx glu ser ser thr -
                thr val gln ser arg asn ile cyx asp ile ser cyx asp -
                lys leu leu asp asp asp ile thr asp asp ile met cyx -
```

```
                val lys lys ile leu asp ile lys gly ile asp tyr trp -
                leu ala hid lys pro leu cyx ser asp lys leu glu gln -
                trp tyr cyx glu ala glne end
        build cross name alc resn 6 atna sg resn 120 atna sg -
              name alc resn 28 atna sg resn 111 atna sg -
              name alc resn 73 atna sg resn  91 atna sg -
              name alc resn 61 atna sg resn  77 atna sg
quit
setmodel
  read parm file paramstd.dat noprint
  enrg parm cutoff 78.0 diel 1.0 nodist listupdate 10
  setp
   mmec
  quit
quit

put 1 into 'counter'
while 'counter' le 880

!  Build filename from counter value
put ($gpla_$ concat (concat (char 'counter') $.pdb$ )) into 'pdbfile'
!  Use create task to read pdb file
create
        read coord impact name alc file 'pdbfile'
quit

reset 'cord'
reset 'com'
reset 'r2'
reset 'sr'
reset 'top'
reset 'rg'

!! Calculate center of mass
put sum 'mass' into 'tmass'
put 'cord' * 'mass' into 'temp'
put sum 'temp' into 'stemp'
put 'stemp' / 'tmass' into 'com'
!show 'com'
!! Sum squared coordinates with com removed
put 'cord' - 'com' into 'r2'
put 'r2' * 'r2' into 'r2'
put 'r2_x' + 'r2_y' into 'sr'
```

```
put 'sr' + 'r2_z' into 'sr'
!show 'sr'
!! Calculate radius of gyration
put 'sr' * 'mass' into 'top'
put 'top' / 'tmass' into 'rg'
put sum 'rg' into 'rg'
put 'rg' pow 0.5 into 'rg'
!show 'rg'
put 'rglist' append 'rg' into 'rglist'                  ! collect data
put 'time' append 'counter' into 'time'                 ! at each psec

put 'counter' + 1 into 'counter'
endwhile

table
        plot 'time' 'rglist' tabular file rg.dat
quit

end
```

6 Trouble Shooting

This chapter describes some common problems with starting or running Impact. Naturally, we hope that you will never need to use this chapter. However, if you have problems using Impact, you may find useful advice here. You may also contact us using the information on the cover page.

6.1 Problems Getting Started

This section describes how to overcome some problems in starting up your Impact jobs. The next section describes problems that occur during job execution.

6.1.1 Environment variable SCHRODINGER not set.

Before running Impact, or any Schrödinger product, on any particular machine, you must set the environment variable SCHRODINGER to your Schrödinger installation directory. If this environment variable is not set correctly, you will be told directly:

```
unix% /usr/apps/schrodinger/impact -i dynamics_job.inp
ERROR: SCHRODINGER is undefined
unix%
```

Or if the program stops at automatic atom-typing for ligand molecules, it will prints out message like this:

```
%IMPACT-I (readhead): input file  23 has no header information.
%IMPACT-I (readhead): input file  23 has no header information.
 PARM read from file paramstd.dat
Environment variables MMSHARE_EXEC and OPLS_DIR not defined
Set OPLS_DIR so that ATOMTYPE can find data files
```

It is easy to fix this problem, first check whether SCHRODINGER is set or not, enter the command

```
% echo $SCHRODINGER
```

If you see this environment variable is not set or set to a wrong directory, change it to a right directory. If you are running C shell (csh) or tcsh, type the command

```
% setenv SCHRODINGER your Schrödinger installation directory
```

or if you are using bash, sh or ksh, type the command

```
% export SCHRODINGER=your Schrödinger installation directory
```

6.1.2 Bad residue label

The current Impact program requires the user to separate a ligand molecule from the protein in the input PDB files. This means PDB files for proteins must contain only the regular amino acids and buried waters, but not a

nonstandard residue name unless it has previously been defined. Here is an example of a PDB file containing a residue named NOA (NAPHTHYLOXY-ACETYL):

```
.............
.............
ATOM   1485  CD2 NOA I 201       4.098   9.733  20.948  0.50 20.67
ATOM   1486  CD1 NOA I 201       6.413  10.411  21.013  0.50 20.84
ATOM   1487  CE1 NOA I 201       6.706   9.320  21.850  0.50 21.17
ATOM   1488  CZ1 NOA I 201       5.694   8.437  22.228  0.50 20.95
ATOM   1489  CE2 NOA I 201       4.385   8.645  21.778  0.50 21.01
ATOM   1490  CZ3 NOA I 201       1.771   9.028  20.869  0.50 21.10
ATOM   1491  CE3 NOA I 201       2.786   9.926  20.504  0.50 20.98
ATOM   1492  CZ2 NOA I 201       3.379   7.740  22.165  0.50 21.13
ATOM   1493  CH2 NOA I 201       2.067   7.934  21.703  0.50 21.20
ATOM   1494  C   NOA I 201       4.312  13.086  17.860  0.50 18.24
ATOM   1493  CH2 NOA I 201       2.067   7.934  21.703  0.50 21.20
ATOM   1494  C   NOA I 201       4.312  13.086  17.860  0.50 18.24
ATOM   1495  O   NOA I 201       5.155  13.679  17.160  0.50 17.86
.............
.............
```

The program will stop because (we presume) there is no template file for residue NOA. The message printed out in the primary output file looks like this:

```
      *** BAD RESIDUE LABEL    NOA
%IMPACT-E (die): Fatal error at line   5
```

At present, the user has to separate the NOA molecule from the protein residues in the PDB file, and read it in through `type ligand`:

```
build primary name hiv type protein read file hiv.pdb
build primary name noa type ligand read file noa.pdb
```

6.2 Runtime Problems

This section documents some situations when an Impact job may terminate prematurely.

6.2.1 SHAKE problems

`SHAKE` is a commonly used algorithm for constraining bond lengths and (or) bond angles in protein or solvent molecules, such as water. It is especially useful for rigid water models such as SPC, TIP3P, and TIP4P. However, the algorithm is only useful for small perturbations from their equilibrium values. If the bond lengths are too far away from their equilibrium values, the algorithm will encounter problems with numerical instability:

```
%IMPACT-W (ishake): SHAKE was not accomplished within   1000 iterations
```

```
%IMPACT-W (ishake): SHAKE was not accomplished within   1000 iterations
%IMPACT-W (ishake): SHAKE was not accomplished within   1000 iterations
```

The problem is usually due to a too-large timestep in molecular dynamics, or the molecular structure is not well minimized. Thus, extremely large repulsion forces might appear in van der Waals interactions, which results in a large move in bond lengths. The way to avoid this problem is to check your structure first, make sure it is well defined and minimized to some extent, then try again. If it still fails, use smaller time steps.

6.2.2 FMM problems

If you specify `fmm` in `setmodel` task, the program will call the FMM method for calculating electrostatic interactions. Here is a common problem:

```
%IMPACT-W(FMM_load_bodies): particle out of box in FMM
%IMPACT-W(FMM_load_bodies): particle out of box in FMM
%IMPACT-W(FMM_load_bodies): particle out of box in FMM
%IMPACT-E(FMM_load_bodies) Too many particles out of box, check your timestep!
```

The problem usually appears when some particles move too much inside one `r-RESPA` big time step (or one `VERLET` time step). The box size, which is updated after every big time step in `r-RESPA`, might not be large enough to hold all the particles, thus some particles move out of the range of box size. Of course, the real underlying reason for this problem is similar to that in `SHAKE`, a too-large timestep in molecular dynamics, or an ill-defined molecular structure is used. Thus, the way to avoid this problem is similar to that in SHAKE, i.e., check your structure first, make sure it is well defined and minimized to some extent, then try again. If the problem still appears, use smaller time steps.

6.2.3 Atom overlap problems

The program may stop if two or more atoms overlap in space. Impact checks for atom overlaps in the very beginning when non-bonded lists are generated. Here is one example error message:

```
%IMPACT-I(code): found all bond parameters for system
%IMPACT-I(code): found all bend parameters for system
%IMPACT-I(code): found all tors parameters for system
  Moment of inertia tensor
          0.46449E+07     0.90790E+06     0.87475E+06
          0.90790E+06     0.45322E+07    -0.61956E+06
          0.87475E+06    -0.61956E+06     0.43931E+07
  Moment of inertia tensor after diagonalizing
          0.29204E+07     0.90495E-10     0.17211E-08
          0.90495E-10     0.50757E+07    -0.17493E-08
          0.17211E-08    -0.17493E-08     0.55741E+07
```

```
  Maximum distance along x,y,z-axis
          0.61017E+02     0.38485E+02     0.35377E+02
  Solutes are rotated 90 degree about y-axis
  Maximum distance along x,y,z-axis after the rotation
          0.35377E+02     0.38485E+02     0.61017E+02
 %IMPACT-I (trans): The system will be rotated to align the principal
                    axis with the largest eigenvalue along the diagonal
  Maximum distance along coordinate axis after the rotation
          0.46611E+02     0.44300E+02     0.45865E+02
%IMPACT-I (allocnb): Verlet list size =   261232
%IMPACT-I (allochb): Hydrogen bond list size =   206421
%IMPACT-E (die): At line  29
%IMPACT-E: TWO ATOMS HAVE THE SAME COORDINATES
```

The program stops because it finds that two or more atoms overlap. This may happen when missing H atoms generated by Impact sit on top of other H atoms that already exist in a PDB file (usually those H atoms were generated by other programs, such as Macromodel or ChemEdit, etc.). Another possible cause of this problem is that some atoms' coordinates were not initialized to correct values, but are all zero. This is especially likely to happen in simulations with explicit solvent. The program needs to know the coordinates of solvent water molecules either by reading from a restart file or by reading from an old equilibrated water box (e.g., *spchoh.dat*, *tip4p.dat*). If a restart file is not used, no water atom coordinates will be assigned and FORTRAN code will initialize them all to zero. Thus they "overlap" in space. Here is an example of an incorrect input file:

```
!! Timings for testing protein/water system
write verbose 3 file test.out title test *

CREAT
  build primary name test type protein read file test.pdb
  read coordinates name test brookhaven file test.pdb
  build solvent name agua type spc nmol 10000 h2o
QUIT

SETMODEL
   setpotential
     mmechanics
   quit
   energy molcutoff name agua
   read parm file paramstd.dat noprint
!==>  solvent old file spchoh.dat bx 68 by 68 bz 68
   solute translate rotate diagonal
   enrg parm cutoff 9.0 -
     listupdate 20 diel 1.0 nodist print 1
```

```
   enrg periodic name test bx 68 by 68 bz 68
   enrg periodic name agua bx 68 by 68 bz 68
   enrg cons bond
QUIT

MINIMIZE
 input cntl mxcyc 1000
 steepest dx0 0.01 dxm 1.0
!==>  read restart box coordinates formatted file testh2o.min
 run
 write restart box coordinates formatted file testh2o.min
QUIT

END
```

The solution is to uncomment either of the two commented out (!==> ****) command lines.

6.2.4 Atomtyping problems

The automatic atomtyping code will assign atom types and parameters for virtually any kind of molecule or ion if the structure is well defined, i.e., if all missing H atoms are included and bond lengths are reasonable. If a structure is not well defined, i.e., if there are too many isolated atoms or too many atoms with bonds exceeding their maximum numbers, the atomtyping code will get confused. Here is an example of an output message:

```
%IMPACT-I(newres): Input template file is a PDB file
%IMPACT-I(newres): build template for this molecule

Warning: too many bonds for atom   H25 : nconn=2 max=1
Warning: too many bonds for atom   H26 : nconn=3 max=1
Warning: too many bonds for atom   H27 : nconn=3 max=1
Warning: atom   H30 is isolated
Warning: atom   H31 is isolated
Warning: atom   H32 is isolated
Warning: atom   H33 is isolated
Warning: too many bonds for atom   H37 : nconn=2 max=1
Warning: too many bonds for atom   H38 : nconn=2 max=1
Warning: too many bonds for atom   H40 : nconn=2 max=1
Warning: too many bonds for atom   H41 : nconn=2 max=1
Warning: atom   H42 is isolated
Warning: atom   H43 is isolated
Warning: atom   H44 is isolated
Error: Too many exceptions in connection table, check your molecule
```

Impact will try to adjust the connection table to resolve these issues, but will stop if too many problems are encountered. Such problems can occur when structures are used that have been converted from other programs, especially structures converted from 2D to 3D. A solution may be to use a program that has a builder, such as Maestro or ChemEdit, to rebuild the molecule.

Appendix A Impact Data and Parameter Files

This appendix describes some of the auxiliary files that come with Impact.

A.1 Datafile Info

Summary of Impact data files:

- Residue database files: These files contain structural information for residues that have been predefined for use in Impact.
- Energy parameter files: These files contain the parameters for the energy functions. The file '`paramstd.dat`' contains the current parameters.
- Boxes of water: The file '`spchoh.dat`' contains a coordinate set for 216 water molecules with a periodic box size of 18.6206^3 $Å^3$.

A.2 Residue Database Description

The purpose of this section is to give a description of the residue database, which consists of the formatted files that are described below. The database presently contains the data files for the 20 L-amino acids, the D- and R-nucleotides, water, and other common groups that are important in molecular modeling. Any user defined residue must be in the same format. The data is expected in the given order although it is possible to use free format as long as the order of the numbers is correct. User defined residues may be created using the `make` subtask in task `create`. All the residues are specified by their three letter amino acid code, and any new residues may be created using the same format as shown below. Because this portion of Impact is is written in FORTRAN, the `format` statements appropriate to the datatabase files are shown as well. They are set off from the text using boxes.

A.2.1 Residue File Example

The formatted residue file for `ALA` is shown below. Note that the program has been modified to allow free-format residue template files. Thus, the restrictive fixed-field format shown below is no longer necessary; this is especially helpful if you want to build a template file by hand.

```
* DATABASE FILE FOR ALANINE
*
ALA    10    9   14   17   39
    1    0 M   N   N      10    1.335000  116.600000  180.000000
    2    1 E   H   HN      2    1.010000  119.800000    0.000000
    3    1 M   CT  CA     10    1.449000  121.900000  180.000000
```

```
   4    3 E   HC  HA      4    1.090000  109.500000  300.000000
   5    3 3   CT  CB      8    1.525000  111.100000   60.000000
   6    5 E   HC  HB1     6    1.090000  109.500000   60.000000
   7    5 E   HC  HB2     7    1.090000  109.500000  180.000000
   8    5 E   HC  HB3     8    1.090000  109.500000  300.000000
   9    3 M   C   C      10    1.522000  111.100000  180.000000
  10    9 E   O   O      10    1.229000  120.500000    0.000000
-0.4630  0.2520  0.0350  0.0480 -0.0980  0.0380  0.0380  0.0380
 0.6160 -0.5040
  9   4   7   6   5   3   2   1   1   1
  2   3   4   5   6   7   8   9  10
  3   4   5   9
  4   5   6   7   8   9  10
  5   6   7   8   9  10
  6   7   8   9  10
  7   8   9
  8   9


  9
 10
  0
  1   2       1   3       3   4       3   5       3   9       5   6
  5   7       5   8       9  10
  1   3   4       1   3   5       1   3   9       2   1   3       3   5   6
  3   5   7       3   5   8       3   9  10       4   3   5       4   3   9
  5   3   9       6   5   7       6   5   8       7   5   8
 -1   3   1  -2       1   3   5   6       1   3   5   7       1   3   5   8
  1   3   9  10       2   1   3   4       2   1   3   5       2   1   3   9
  3  11   9 -10       4   3   5   6       4   3   5   7       4   3   5   8
  4   3   9  10       5   3   9  10       6   5   3   9       7   5   3   9
  8   5   3   9
```

(The FORTRAN `format` statement for each line is indicated underneath the verbatim listing.)

A.2.2 Title card

```
* TITLE CARD (S)
*
```

```
A80
```

A blank line indicates end of title cards.

A.2.3 Residue name

```
ALA    10    9   14   17   39
```

```
(A4,5I5)
```

This is the first line of the file. It contains the residue name as it will appear in the input for `create`. This is followed by the number of atoms, the number of bonds, bond angles, and torsion angles. Finally, the total number of nonbonded exclusions (described below) appears in this line.

A.2.4 Tree structure

```
 1    0 M   N   N      10    1.335000  116.600000  180.000000
 2    1 E   H   HN      2    1.010000  119.800000    0.000000
 3    1 M   CT  CA     10    1.449000  121.900000  180.000000
 4    3 E   HC  HA      4    1.090000  109.500000  300.000000
 5    3 3   CT  CB      8    1.525000  111.100000   60.000000
 6    5 E   HC  HB1     6    1.090000  109.500000   60.000000
 7    5 E   HC  HB2     7    1.090000  109.500000  180.000000
 8    5 E   HC  HB3     8    1.090000  109.500000  300.000000
 9    3 M   C   C      10    1.522000  111.100000  180.000000
10    9 E   O   O      10    1.229000  120.500000    0.000000
```

```
(2I5,1X,3A4,I5,3F12.6)
```

This section contains information about the tree structure of the amino acid. The first column is the atom number. The second column is the atom that atom i is joined to (`ijoin`). The third number represents what position the atom holds in the tree structure (`M`-main chain atom, `S`-side chain atom, `B`-branch atom, 3-three-way branch atom, `E`-end atom). The fourth column is the atom type (used to match entries in the parameter file). The fifth

column is the unique atom name (or graph name). The next column contains a variable (`rotat`) that can best be described as the number of the last atom that is affected if the atom in question is rotated. Finally this is followed by the r, θ and ϕ for this atom.

A.2.5 Charges

```
-0.4630  0.2520  0.0350  0.0480 -0.0980  0.0380  0.0380  0.0380
 0.6160 -0.5040
```

```
(8F8.4)
```

This line contains the charge for each atom of the residue.

A.2.6 Nonbonded array

```
 9   4   7   6   5   3   2   1   1   1
```

```
(16I4)
```

This line contains the pointer into the nonbonded array. It says how many nonbonded exclusions each atom has in the excluded atom array. See explanation below.

A.2.7 Excluded atom array

```
 2   3   4   5   6   7   8   9  10
 3   4   5   9
 4   5   6   7   8   9  10
 5   6   7   8   9  10
 6   7   8   9  10
 7   8   9
 8   9
 9
10
 0
```

```
(16I4)
```

This is the excluded atom array. A new line is used for the nonbonded exclusions for each atom to aid the user. The excluded atom array lists atoms to which one does not want to calculate nonbonded interactions. Typically,

these are atoms that are 3 or fewer bonds away from the original atom and that are involved in bond, angle or torsion interactions. The list moves down the tree so that if one does not want to calculate the nonbonded interaction between atoms 4 and 6, line number four of the list would include 6, but line number six of the list would not include 4.

A.2.8 Bonded atom list

```
 1   2      1   3      3   4      3   5      3   9      5   6
 5   7      5   8      9  10
```

```
(6(2I4,3X))
```

These lines contain all pairs of atoms that are bonded to each other. As many lines as needed can be used.

A.2.9 Bond angles

```
 1   3   4      1   3   5      1   3   9      2   1   3      3   5   6
 3   5   7      3   5   8      3   9  10      4   3   5      4   3   9
 5   3   9      6   5   7      6   5   8      7   5   8
```

```
(5(3I4,3X))
```

These lines contain the angles for this residue.

A.2.10 Dihedral angles

```
-1   3   1  -2      1   3   5   6      1   3   5   7      1   3   5   8
 1   3   9  10      2   1   3   4      2   1   3   5      2   1   3   9
 3  11   9 -10      4   3   5   6      4   3   5   7      4   3   5   8


 4   3   9  10      5   3   9  10      6   5   3   9      7   5   3   9
 8   5   3   9
```

```
(4(4I4,3X))
```

These lines contain the dihedral angles for the residue. There are several special meanings for the - sign in a dihedral angle listing.

`-1 x y z` This torsion angle is a torsion angle that connects the current residue to the last main chain atom of the previous residue.

`w x y -z` This is called an improper torsion and is used to help keep the three atoms attached to a central, trigonal atom in the same plane. The proper order of this angle is Cn1 Cn2 C -H, where Cn1 and Cn2 are the neighboring carbons to either side and C is the carbon to which the hydrogen is attached.

`w x -y z` This notation is used to avoid double counting 1,4-interactions in rings of size 6 or smaller; this provision is needed because 1,4-interactions and torsions share the same list within Impact. For an example, if a benzene ring has the six atoms C1, C2, C3, C4, C5 and C6, the possible torsions are: 1 2 3 4; 2 3 4 5; 3 4 5 6; 4 5 6 1; 5 6 1 2; 6 1 2 3. The last three sets are redundant for 1,4-interactions and should be written as follows: 4 5 -6 1; 5 6 -1 2; 6 1 -2 3. The negative sign in the notation for improper torsions (see above) also serves to ensure that these (spurious) "1,4-interactions" are not counted.

A.3 Energy parameter file description

The input for the energy function parameter file for amber86 is free-format and is read by the routine `parmrdr`. Below is an abbreviated version of the file that contains samples of the necessary input. Atom types are always character strings. For cases where more than one atom type is needed, the atom types are separated by a dash (`-`). Numbers are always separated by a space.

- First a title is read. Each card of the title begins with a '`*`' and the last card of the title is a '`*`' followed by one or more spaces.
- Second, the atom types and their atomic masses are read in. Atom type (character data type) followed by the atomic mass in amu and atomic number.
- Third, the bond stretching parameters are read in. This section must begin with `bond` and must be present even if there are no bond parameters to be read. Then the bond parameters are read in. Each record consists of 2 atom types followed by the harmonic force constant and equilibrium distance (units are kcal/mole × Å and kcal/mole, respectively).
- Fourth, the angle bending parameters are read in. This section must begin with `thet`. Then, for each angle parameter 3 atom types are read in followed by the harmonic force constant and the equilibrium angle. The force constant is in kcal/mole-radian and the angle is in degrees.
- Fifth, the proper torsion interactions are read in following the keyword `phi`. The proper torsions as specified by giving by 4 atom types followed

by a divisor n_d, a barrier V_n, a phase (sign), and the periodicity pn. The phase is read in degrees but is immediately converted to a sign by taking the cos(`phase`). The phase should only be 0 or 180. The functional form assumed is

$$e = \frac{V_n}{n_d}\left(1 + \text{sign}\,\cos(pn\phi)\right)$$

where ϕ is the torsional angle. General dihedral types may be specified using `X` instead of specific atom types for the first and last atoms.

- Sixth, the improper torsions are read in. `iphi` is the keyword used to initiate this section. The input is the same as for the proper torsion except that n_d is not read. General improper torsions may be specified by using `X` for the first, second, or fourth positions; the third position corresponds to the "central" atom.
- Seventh, the non-bonded parameters are read in beginning with the keyword `nbon`. The input is the atom type, $\sigma/2$ (half the Lennard-Jones distance at the zero-crossing point), and ϵ (the well depth). Impact calculates and stores 4ϵ. The functional form for the Lennard-Jones interactions is

$$e = 4\epsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right].$$

- Last, for amber86 h-bond parameters are read in beginning with `hbond`. The two atom types are read followed by the A and B parameters. The functional form is

$$e = \frac{A}{r^{12}} - \frac{B}{r^{10}}.$$

The last card must be `end`.

A.4 Energy example

```
* FORMATED PARAMETER INPUT FILE FOR IMPACT20  9/2/87
* PARAMETERS FROM ALLATOM FORCE FIELD OF PETER KOLLMAN 1985
*
BR  79.90
C   12.01
CA  12.02
CB  12.01
BOND
NC  -NC   100.       1.15      AZA  -azide ion resonance appx. ! ADDED TO PAK
S   -OS   100.       1.5       from a crystal stru            !
LP  -S    600.       0.679                                    !
LP  -SH   600.       0.679                                    !
THET
```

```
C2  -C   -N       70.        116.6    GLY            GELIN
C2  -C   -O       80.        120.4    ASN(OL)        GELIN
C2  -C   -O2      70.        117.    GLU(OL)         SCH JPC 79,2379
PHI
X   -C   -C2  -X      2    0.0        180.          3.
X   -C   -CA  -X      4    5.3        180.          2.
X   -C   -CB  -X      4    4.4        180.          2.
X   -C   -CD  -X      2    5.3        180.          2.
IPHI
H2  -CH  -N2  -H2          0.0         180.         3.
C3  -CH  -NT  -C           14.0        180.         3.
CH  -CH  -C   -N3          7.0         180.         3.
C2  -CH  -C   -N3          7.0         180.         3.
C3  -CH  -CA  -C3          7.0         180.         3.
X   -C2  -CH  -X           14.0        180.         3.
X   -CH  -CH  -X           14.0        180.         3.
NBON
H    0.8908987  0.0200000
HO   0.8908987  0.0200000   ***** note that these are sigma/2 and


H2   0.8908987  0.0200000          epsilon (i.e. well-depth)
H3   0.8908987  0.0200000
HBON
H   -O      7557.00   2385.00
H   -OH     7557.00   2385.00
H   -NB     7557.00   2385.00
H   -S    265720.00  35429.00
H   -SH   265720.00  35429.00
END
```

A.5 Units

This chapter explains the units employed in Impact.

1. The use of gram/mole (g), Ångstrom (Å) and picosecond (psec) do not naturally lead to kcal/mole, which is consistently employed for the

Quantities	Unit (abbrev.)	Relation with other units
length	Å	10^{-8} cm
angles	degree (°)	$180° = \pi$ rad
time	picoseconds (psec)	10^{-12} s (1)
mass	$\frac{\text{gram}}{\text{mole}}$ (g)	
energy	$\frac{\text{kcal}}{\text{mol}}$	4.18 $\frac{\text{kjoule}}{\text{mol}}$
force	$\frac{\text{kcal}}{\text{Å mol}}$ (bonds)	
	$\frac{\text{kcal}}{\text{rad mol}}$ (angles)	
force constants	$\frac{\text{kcal}}{\text{Å}^2\ \text{mol}}$ (bonds)	
	$\frac{\text{kcal}}{\text{rad}^2\ \text{mol}}$ (angles)	
charge	$\sqrt{\frac{\text{Å kcal}}{\text{mole}}}$	$1.0\,\text{esu} = 3.794 \cdot 10^{10}\sqrt{\frac{\text{Å kcal}}{\text{mole}}}$ (2)
Lennard-Jones σ	Å (3)	
Lennard-Jones ϵ	$\frac{\text{kcal}}{\text{mol}}$ (3)	

energy parameter in Impact. Namely,

$$\begin{aligned} 1\frac{\text{kcal}}{\text{mole}} &= \frac{4.184 \cdot 10^{10}\,\text{erg}}{\text{mole}} \\ &= 4.184 \cdot 10^{10}\,\frac{\text{g cm}^2}{\text{sec}^2} \\ &= 4.184 \cdot 10^{10}\text{g}\,(10^8\ \text{Å})^2/(10^{12}\,\text{psec})^2 \\ &= 4.184 \cdot 10^{2}\text{g}\,\text{Å}^{\,2}/\text{psec}^2. \end{aligned}$$

That is, if you use psec for time, your energy expression is a factor $4.184 \cdot 10^2$ off. Therefore, conversion has been made for the time step

(and the relaxation time for the temperature scaling) in the program so that the factor is canceled. The conversion factor is $\sqrt{4.184 \times 100}$ (see Section 3.2 [Dynamics], page 77).

2. $$\begin{aligned} 1\text{esu} &= \sqrt{\text{cm erg}} \\ &= \sqrt{10^8\,\text{Å}\,6.023 \cdot 10^{23}\,\text{erg/mole}} \\ &= \sqrt{10^8\,\text{Å}\,6.023 \cdot 10^{23}/10^{10}\,\text{kjoule/mole}} \\ &= \sqrt{10^8\,\text{Å}\,6.023 \cdot 10^{23}/(10^{10} \times 4.184)\,\text{kcal/mole}} \\ &= 3.794 \cdot 10^{10}\sqrt{\text{Å kcal/mole}} \end{aligned}$$

   Electronic charge:

$$\begin{aligned} 4.80296 \cdot 10^{-10}\text{esu} &= (4.80296/10^{10})(3.794 \cdot 10^{10})\sqrt{\text{Å kcal/mole}} \\ &= 18.223\sqrt{\text{Å kcal/mole}} \end{aligned}$$

3. The formula for Lennard-Jones interaction is:

$$U(r) = 4\epsilon\left\{\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right\}$$

   where σ is the interatomic distance at which $U(r) = 0$, and ϵ is the depth of the potential.

Appendix B Task Plot

Because it is expected that `plot` will significantly change or be replaced in a future release, it has been relegated to the appendix.

B.1 Subtask Plot

The object of this subtask is to parse data necessary for the the plotting routines used in Impact. In order to get a plot, all that is necessary to type is the word `plot`; the remaining parameters are set to defaults that should give you a reasonable plot. All the plotting commands listed below are used in a standard manner throughout Impact.
Several devices are supported:

- `plot [ lineprint [ file` *filnam* `] | [ postscript | delay | tabular ]  file` *filnam*

`Lineprint` causes output to be generated for a wide cartridge ascii line printer device (or any text output device with 132 columns) and, of course, it uses dot graphics. The `postscript` device is only for line graphics. The only other device-specific option available is `paper`. Note that you can not mix devices within the same `plot` subtask, and that the `file` option should always be used for device `postscript`, while it is optional for the device `lineprint`. The keyword `delay` should be specified when the data is generated, and must include the file to which to write the plot-data output; the resultant formatted data file can be read into Impact using the `read` option. Similarly, the keyword `tabular` instructs Impact to output the data in a simple tabular form, as expected by many modern packages. Notice that no information about titles, legends, etc., is preserved with this format.

- `plot [ portrait | landscape ] [ small | large ]`

`Portrait` is the default, and this option selects the vertical side to be the long axis in an 8 by 11 printout. The option `landscape` rotates the plot 90 degrees. Note that you must specify either `small` or `large` with this option. `Small` is the default, and equally scales the x and y axes, while the keyword `large` scales the X and Y axes to use as much of the papers surface as available. (Margins of at least one inch are always maintained). The labels for the axes and a title can be specified as arguments to the keywords `title`, `xlabel` and `ylabel`. Titles appear on the top of the plots.

- `plot title` *string* `xlabel` *x-label* `ylabel` *y-label*

The way numerical labels are printed on the axis can be controlled with the keywords `scientific`, `field1` and `field2`. The first, as its name implies, forces scientific notation to be used; the latter two control the number of characters before and after the decimal place (default to 5 and 3, respectively).

- `plot scientific [ field1` *num* `field2` *num* `]`

The appearance of tick marks on the axis can be further controlled with the keyword `nice`. When set to 1, the program places tick marks at even

values, and if set to 0 it places tick marks at evenly divided points between minimum and maximum values. (This works only for dot graphics.)

- `plot nice [ 0 | 1 | nil ] -`
  `xmin` *xmin* `xmax` *xmax* `-`
  `ymin` *ymin* `ymax` *ymax*

When plotting on a character device the user should issue the `point` command, which takes an optional keyword to choose the character to be used for the plots. The keyword `key` causes a table of keys to be printed in the upper right hand corner. The the contour values are printed along with the Greek and Roman symbols that mark each value in the contour graph.

- `plot point [ scharacter` *number* `| ccharacter` *character* `] -`
  `[ key | nokey ]`

When plotting on a line device this command should be used.

- `plot curve`

Contour plots can also be generated.

- `plot contour` *contours* `[ automatic | at` list of values `] -`
  `[ vmin` *vmin* `vmax` *vmax* `]`

The keywords `vmin` and `vmax` set the minimum and maximum values for the data that will be contoured (the the program will automatically calculate these values if they are not provided). The keyword `automatic` makes the number of contours set with `contour` evenly spaced between `vmin` and `vmax`. If `at` is followed by a list of values, they will instead be used to generate the contours.

Three-dimensional plots seem also possible.

- `plot surface [ level2d | level3d ] [ framed ] -`
  `[ theta` *theta* `phi` *phi* `distance` *d* `]`

The keyword `surface` selects a hidden-line-removal algorithm. The keywords `level2d` and `level3d` control how 'fancy' the plot will be: for `level2d` a plot of the data is put on the top half of the page and a the corresponding 2D contour graph drawn as a plane is drawn on the bottom half of the page. For `level3d`, a model of the current molecule is plotted on the top third of the page. In the middle third a surface graph is placed and on the bottom third the corresponding 2D contour graph drawn as a plane is drawn. Note the the graph's generating structural data must accompany the graph. The keywords `theta`, `phi` and `distance` set the viewpoint that is used to generate the 3D plot. `Theta` is given in degrees, and refers to the viewers rotation along the x axis. The default is 40°. `Phi` is given in degrees, and refers to the viewers rotation along the y axis. The default is 40°. `Distance` sets the distance of the viewer from the projection plane used in surface graphs. Using a movie projection screen as an model, the further away from the projector, the larger the image will be. The default is 800.0 (data is normalized to 800 and should fill the surface with some room to spare). Note that this option will not work with `level2d` and `level3d` options. If `framed` is found, the program frames the graph with four vertical lines marking the edges of

a surface graph, and prints a two point scale indicating highest and lowest values in the surface. (This can make understanding the surface graph much easier.)

B.2 Subtask Read

This subtask reads a file of plottable data. The options `1d` and `2d` read, respectively, data for (a) $x - y$ plots or (b) for contour or 2-dimensional plots. Both `formatted` or `unformatted` files can be specified. The option `number` allows reading data for the plot number specified when multiple files are included in the input.

- `read [ 1d | 2d ] [ formatted | unformatted ] file` *fname* `number` *num*

B.3 Subtask Write

Write a file of plottable data in a format consistent with the read subtask.

- `write [ 1d | 2d ] [ formatted | unformatted ] file` *fname*

B.4 Subtask Rewrite

This subtask writes a file of plottable data in a tabular format consistent with a number of plotting packages, e.g., Cricketgraph for the Macintosh.

- `rewrite formatted file` *fname*

The file *fname* would have the format:

n (number of points)
`x_1 y_1`
`x_2 y_2`
...
`x_n y_n`

B.5 Subtask Reread

Read a file of plottable data in a tabular format consistent with other plotting software (such as Cricketgraph on the Macintosh).

- `reread formatted file` *fname*

Appendix C Example Input Files

This appendix contains a variety of example input files showing how Impact is used. It is hoped that this will aid both new and experienced users by providing templates that can be modified to suit their needs. It should be noted, however, that the selection is not complete, i.e., not all tasks and subtasks are well represented.

Each example is in its own section and begins with a commented input file that has been specially formatted and annotated. These input files and the corresponding Impact output files are distributed with the Impact software package in the examples directory.[1]

[1] See the FirstDiscovery Installation Guide for details.

C.1 Tutorial Examples

This section illustrates some basic Impact simulations

C.1.1 OPLS Minimization

This example demonstrates the use of the OPLS all-atom force field (OPLS-AA) in Impact. We read in a PDB-format file containing coordinates of the "c7eq" conformation of the so-called alanine dipeptide (Acetyl-Alanyl-N-Methylamide), minimized using OPLS-AA in another program. This program calculated an energy of -41.8747 kcal/mol for this conformation.

Input files	
`c7eq-opls.inp`	Main input file
`c7eq.pdb`	Initial coordinate file
`paramstd.dat`	Parameter file

Output files	
`c7eq-opls.out`	Main output file
`c7eq-opls_min.pdb`	Minimized structure file

The `set ffield` command tells Impact to use the functional form of the OPLS force field, and to find residue and parameter files in the appropriate directory.

```
set ffield opls
write file c7eq-opls.out -
      title OPLS Minimization of Alanine dipeptide c7eq conf*
```

Note that the residue names in the `build primary` command, and the parameter file name in `read parm`, are the standard ones. The database directory for OPLS contains files with the same names as those in the default directory, but the contents of these files are the topologies and parameters appropriate to OPLS.

```
create
  build primary name ala2 type protein -
  ace ala nma end
  read coordinates brookhaven name ala2 file c7eq.pdb
  build types name ala2
quit
setmodel
  setpotential
```

```
    mmechanics
  quit
  read parm file paramstd.dat noprint
  energy parm cutoff 100.0 listupdate 10 dielectric 1.0 nodistance print 10
quit
```

Measure the phi, psi, and chi angles for the alanine residue, for later comparison.

```
analysis
  measure
    calc tors resnumber 1 atomname c resnumber 2 atomname n -
              resnumber 2 atomname ca resnumber 2 atomname c -
         tors resnumber 2 atomname n resnumber 2 atomname ca -
              resnumber 2 atomname c resnumber 3 atomname n -
         tors resnumber 2 atomname n resnumber 2 atomname ca -
              resnumber 2 atomname cb resnumber 2 atomname hb1
  quit
quit
```

Performing energy minimization serves two purposes. "Step 0" of the minimization gives the energy of the initial conformation, which can be compared to that calculated by the other program. The subsequent minimization should confirm that the minimum found by Impact is essentially the same as the initial conformation. Neither the energy nor the geometry (as measured by the torsions and by RMS coordinate deviations) should change significantly.

```
minimize
   conjugate
   input cntl mxcyc 10000 rmscut 1.0e-4 deltae 1.0e-7
   run
   write pdb brookhaven name ala2 file c7eq-opls_min.pdb
quit
analysis
  measure
```

Recalculate the torsions in the final state.

```
! phi, psi, and chi1 for alanine
    calc tors resnumber 1 atomname c resnumber 2 atomname n -
              resnumber 2 atomname ca resnumber 2 atomname c -
         tors resnumber 2 atomname n resnumber 2 atomname ca -
              resnumber 2 atomname c resnumber 3 atomname n -
         tors resnumber 2 atomname n resnumber 2 atomname ca -
              resnumber 2 atomname cb resnumber 2 atomname hb1
  quit
```

Calculate RMS deviations between the final and initial states, first for all atom coordinates and then for the peptide backbone.

```
  rms name ala2 name ala2init pdb2 file c7eq.pdb compare all
  rms name ala2 name ala2init pdb2 file c7eq.pdb compare bone -
      print none
quit
end
```

C.1.2 Solvation Energy of Small Organic Molecules

This example illustrates the solvation energy calculation using continuum solvation model pbf and sgb. Six small organic molecules are used for illustration here, acetamide, acetone, benzene, dimethylamine, ethanol, and methanol.

Input files	
`acetone.inp`	Main input file
`paramstd.dat`	Parameter file
`acetone.pdb`	PDB coordinate file

Output files	
`acetone.out`	Main output file

```
write file acetone.out -
      title acetone solvation energy *
create
   build primary name dim type auto read pdb file acetone.pdb
   build types name dim
```

Set up the simulation system by using type auto to read the pdb file. The second command performs automatic atomtyping on the molecule.

```
quit
setmodel
  setpotential
    mmechanics consolv pbf
```

Select the continuum solvation model, pbf. If user wants to use sgb model, simply change "pbf" to "sgb".

```
  quit
  read parm file paramstd.dat noprint
  energy parm cutoff 20.0 listupdate 10 diel 1.0 nodist
quit
minm
  conjugate dx0 0.05 dxm 1.0 rest 50
```

```
  input cntl mxcyc 1 rmscut 5.0e-3 deltae 1.0e-5
  run
quit
```

Just run one step minimization (actually no minimization is needed) to get the solvation energy for the given structure. If the solvation energy of the minimized structure is desired, then change "mxcyc 1" to a large number.

```
end
```

C.1.3 Dipeptide/H2O MD Simulation at Constant Energy

This example illustrates the preparation of a protein/water system composed of the dipeptide ALA-GLY and a box of 216 SPC-type water molecules. Once the coordinate structures are built the energy minimization and molecular dynamics tasks are performed. In this example the system is prepared for a constant energy Molecular Dynamics simulation.

Input files	
`dipepce.inp`	Main input file
`spchoh.dat`	Solvent coordinate file
`paramstd.dat`	Parameter file
`spcconst.dat`	Constraint file

Output files	
`dipepce.out`	Main output file
`dipepce.rst`	Coordinate and velocity restart file

```
write file dipepce.out -
     title Dipeptide/H2O MD Simulation at Constant Energy *
```

Task `create` is used to build the initial dipeptide/water structure.

```
create
  build primary name dipep type protein ala gly end
  build solvent name solvent1 type spc nmol 216 h2o
quit
```

Task `setmodel` initializes the energy function for this calculation. The coordinates of a 18.6206 Å cube of solvent in this example are read from the file, '`spchoh.dat`'. Periodic boundary conditions will be applied to nonbonded interactions between solvent molecules and nonbonded solute-solvent interactions. Nonbonded energy calculations between solvent molecules will use

a molecular cutoff, and all nonbonded interactions will use a cutoff distance of 8.5 Å. A smoothing function will be used to keep the total energy constant. `SHAKE` constraints for molecular dynamics are read from the file '`spcconst.dat`'.

```
setmodel
  setpotential
    mmechanics
  quit
  read parm file paramstd.dat noprint
  solute translate
  solvent old file spchoh.dat bx 18.6206 by 18.6206 bz 18.6206
  energy parm cutoff 8.5 listupdate 10 diel 1.0 nodist
  energy periodic name solvent1 bx 18.6206 by 18.6206 bz 18.6206
  energy molcutoff name solvent1
  energy constraint read file spcconst.dat
quit
```

The system is minimized prior to the Molecular Dynamics simulation. A 0.1 psec simulation will be run, and energy values will be printed out every 10 steps. If needed, average energy statistics for the dynamics could be obtained using the `statistics` option.

```
minm
  steepest dx0 0.05 dxm 1.0
  input cntl mxcyc 10
  run
quit
dynamics
  input cntl -
      nstep 100 delt 0.001 relax 0.01  -
      stop rotations -
      initialize temperature at 298.0  seed  100 -
      constant totalenergy -
      nprnt 10  tol 1.e-7
  run
  write restart coordinates and velocities box formatted file dipepce.rst
quit
end
```

C.1.4 Dipeptide/H2O MD Simulation at Constant Pressure

This example illustrates the preparation of a protein/water system composed of the dipeptide ALA-GLY and a box of 216 SPC-type water molecules. Once the species are built the coordinates and velocities are read from a

restart file, and molecular dynamics is performed. In this example the system is prepared for a constant pressure molecular dynamics simulation. For a constant pressure simulation, the isothermal compressibility (`dvdp`), effective density of solute molecules (`dens`), type of volume scaling for solute and solvent (`atscale/cmscale`), and target pressure are needed.

Input files	
`dipepcp.inp`	Main input file
`spchoh.dat`	Solvent coordinate file
`paramstd.dat`	Parameter file
`spcconst.dat`	Constraint file
`dipepcp.rst`	Coordinate and velocity restart file

Output files	
`dipepcp.out`	Main output file
`finalcp.rst`	Coordinate and velocity restart file

```
write file dipepcp.out -
      title Dipeptide/H2O MD Simulation at Constant Pressure *
create
   build primary name dipep type protein ala gly end
   build solvent name solvent1 type spc nmol 216 h2o
quit
setmodel
   setpotential
     mmechanics tail
    quit
    read parm file paramstd.dat noprint
    solute translate
    solvent old file spchoh.dat bx 18.6206 by 18.6206 bz 18.6206
    energy parm cutoff 7.5 listupdate 10 diel 1.0 nodist
    energy periodic name solvent1 bx 18.6206 by 18.6206 bz 18.6206
    energy molcutoff name solvent1
    energy constraint read file spcconst.dat
quit
dynamics
  input cntl -
      nstep 10 delt 0.001 relax 0.10 taup 0.10 seed 100 stop rotations -
      constant temperature constant pressure -
      nprnt 1  tol 1.e-7 dvdp 4.96e-5 dens 1.3
```

```
  input cntl name solvent1 cmscale
  input cntl name dipep atscale
  input target temperature 298.0 pressure 1.0
  read restart coordinates and velocities box formatted file dipepcp.rst
  run
  write restart coordinates and velocities box formatted file finalcp.rst
quit
end
```

C.1.5 Monte Carlo Refinement of Protein NP-5

This is an example of a refinement using Monte Carlo. It contains commands that perform the following functions:

- Build a protein with disulfide crosslinks.
- Read in protein coordinates from a PDB file.
- Set up a molecular mechanics potential with NOE constraints.
- Measures particular bond angles and lengths.
- Performs a Monte Carlo Simulation.
- Prints out the results in a PDB file.

Input files	
`refine.inp`	Main input file
`np5orig.pdb`	Initial coordinates (PDB format)
`mcdist.noe`	Distance constraint file
`paramstd.dat`	Energy parameter file

Output files	
`refine.out`	Main output file
`np5refine.pdb`	Refined coordinates (PDB format)

```
write file refine.out -
      title Monte Carlo Refinement of Protein NP-5*
```

Task `create` is used to build the primary structure of the protein.

```
create
 build primary name pardihb type protein -
 val phe cyx thr cyx arg gly phe leu cyx -
 gly ser gly glu arg ala ser gly ser cyx -
 thr ile asn gly val arg hid thr leu cyx cyx arg arg end
```

Here, the disulfide crosslinks are added between cystine residues.

```
build crosslink name pardihb -
   resnumber  5 atname sg resnumber 20 atname sg -
   resnumber 10 atname sg resnumber 30 atname sg -
   resnumber  3 atname sg resnumber 31 atname sg
```

Read in the initial coordinates from the Brookhaven PDB format file, '`np5orig.pdb`'.

```
read coordinates name pardihb file np5orig.pdb
quit
```

Task `setmodel` is used to initialize the energy function.

```
setmodel
  setpotential
   mmechanics noforce name pardihb noecon all nobond noangle
```

The NOE distance constraints are read from the file, '`mcdist.noe`'.

```
   constraint name pardihb noec dist file mcdist.noe con1 12 con2 3
```

The torsion constraints are specified with a range of plus or minus 20 degrees.

```
   constraint name pardihb noec tors nsec 2 fres 19 lres 22 -
               tpsi 135. tphi -140. rang 20. -
               fres 25 lres 29 tpsi 135. tphi -140. rang 20.
   weight constraint name pardihb noe 100. tors  0.005
   quit
```

The energy parameters are read from file, '`paramstd.dat`'.

```
   read parm file paramstd.dat noprint
   energy parm cutoff 8.0  listupdate 10 diel 1.0 distance print 5
quit
```

Calculate bond angles (`angle`) and bond lengths (`bond`).

```
analysis
  measure name pardihb
    calc angl resnumber 22 atomname n resnumber 22 atomname hn -
              resnumber 25 atomname o -
         angl resnumber 22 atomname hn resnumber 25 atomname o -
              resnumber 25 atomname c -
         bond resnumber 22 atomname o  resnumber 25 atomname hn -
         bond resnumber 20 atomname o resnumber 27 atomname hn
  quit
quit
```

Perform a 100 step Monte Carlo simulation. The maximum angle change is 0.5 degrees and the maximum angle change is adjusted every 25 steps if needed. Two side chain regions and the entire backbone are varied.

```
montecarlo name pardihb
  param  step 100  size 0.5 freq 25
  sample schain nseg 2 fres 1 lres 10 fres 17 lres 32
```

```
    sample bbone nseg 1 fres 1 lres 33 type all
    calc
  quit
```

Calculate bond angles and bond lengths upon completion of the Monte Carlo calculations.

```
  analysis
    measure name pardihb
      calc angl resnumber 22 atomname n resnumber 22 atomname hn -
                resnumber 25 atomname o -
           angl resnumber 22 atomname hn resnumber 25 atomname o -
                resnumber 25 atomname c -
           bond resnumber 22 atomname o  resnumber 25 atomname hn -
           bond resnumber 20 atomname o resnumber 27 atomname hn
    quit
  quit
```

Print out the final coordinates in a new PDB file, '`np5refine.pdb`'.

```
  create
    print coordinates name pardihb file np5refine.pdb
  quit
  end
```

C.1.6 Building Primary and/or Secondary Protein Structure

This example illustrates the use of task `create` to build the primary and secondary structure of a protein.

Input files	
`build.inp`	Main input file
`gluthione.dat`	Glutathione residue data file

Output files	
`build.out`	Main output file
`primary.pdb`	Coordinate file (PDB format)

```
write file build.out -
      title Building primary and/or secondary protein structure *
```

Task `create` is used to build the primary structure of a simple protein with two chains (the break is specified by '`***`') with verbose printing of coordinate and connectivity information. The initial coordinates of the dipeptide are printed in Brookhaven PDB format in the file '`primary.pdb`'.

```
create
   build primary name mol1 type protein gly gly *** ala ala end
   print structure name mol1 bond angl tors excl
   print ic name mol1 tors
   print coordinates name mol1 file primary.pdb
   print tree name mol1
quit
```

Here, the primary structure of a 5-residue peptide is built first, followed by the subtask `build secondary`, which assigns the backbone angles of residues 1 through 5 to a helical structure, and the side chain torsion angle χ_2 of residue 2 to 150 degrees.

```
create
   build newresidue gth file gluthione.dat
   build primary name mol2 type protein ala leu ala gth ala end
   build secondary name mol2 helix fresidue 1 lresidue 5
   build secondary side name mol2 resnumber 2 -
      chi 2 tor 150.0
   print tree name mol2
quit
end
```

C.1.7 B-DNA Tetramer

This example illustrates the use of task `create` to build the primary and secondary structure of a B-DNA tetramer. The `analysis` subtask `hbond` is used to calculate hydrogen bonding distances between strands and generate an NOE distance constraints. The initial structure is minimized and the final coordinates are written to the file '`bdnamin.pdb`' in Brookhaven PDB format.

Input files	
`bdna.inp`	Main input file
`paramstd.dat`	Parameter file

Output files	
`bdna.out`	Main output file
`bdna.pdb`	Coordinate file (PDB format)
`bdnamin.pdb`	Minimized coordinate file (PDB format)

```
write file bdna.out -
```

```
      title B-DNA Tetramer *
create
   build primary name bdna nopom type DNAB -
         hb ade pom thy pom gua pom cyt he *** -
         hb gua pom cyt pom ade pom thy he end
   build secondary BDNA name bdna
   print coor name bdna file bdna.pdb
   print tree name bdna
quit
analysis
 hbond ucut 5.0 name bdna gener minus 0.5 plus 1.0
quit
setmodel
  energy parm cutoff 6.0 diel 80.0  -
    distance listupdate 10 print 5 hbcut 4.0
  setpotential
   mmechanics
  quit
  read parm file paramstd.dat noprint
quit
minm
  input cntl mxcyc 10
  steep dx0 0.5 dxm 1.0
  run
quit
create
  print coordinates name bdna file bdnamin.pdb
quit
end
```

C.1.8 Simulation from Maestro file

This example shows how to load and perform a simulation of a molecule stored in a structure file in Maestro format.

Input files	
`maestro.inp`	Main input file
`ala.mae`	Maestro structure file

Output files	
`maestro.out`	Main output file
`ala_min.pdb`	PDB structure file after minimization
`ala_min.mae`	Maestro structure file after minimization
`ala_dyn.pdb`	PDB structure file after MD
`ala_dyn.mae`	Maestro structure file after MD

```
write file maestro.out title Reading and Writing Maestro Files *
```

The molecule is loaded from the Maestro file '`ala.mae`' as '`type auto`'. The force field parameters are assigned automatically using the '`build types`' command.

```
create
  build primary name ala type auto read maestro file ala.mae
  build types name ala
quit
```

Standard energy parameters are selected. Notice that the '`read parm`' command is not necessary if atom types are assigned automatically.

```
setmodel
  setpotential
    mmechanics
  quit
  enrg parm cutoff 99.0 listupdate 1000 diel 1.0 nodist print 1
  enrg cons bond
quit
```

A short energy minimization is performed. The minimized structure is then saved in PDB and Maestro formats.

```
minimize
  input cntl mxcyc 100 rmscut 0.01 deltae 1.0e-4
  steepest dx0 0.05 dxm 1.0
  run
  write pdb brookhaven name prot file ala_min.pdb
  write maestro file ala_min.mae
quit
```

A short MD simulation is performed, after which the structure is saved in PDB and Maestro formats.

```
dynamics
  input cntl nstep 100 delt 0.001 relax 0.01 nprnt 1 seed 101 -
    constant temperature initialize temperature at 10.0
  input target temperature 300.0
  input cntl statistics on
  run rrespa fast 2
  write pdb brookhaven name ala file ala_dyn.pdb
  write maestro file ala_dyn.mae
```

```
quit
end
```

C.2 Advanced Examples

C.2.1 Various Frozen Atom Schemes

This example illustrates how to run a simulation using different frozen atom schemes. It not only speeds up the simulation by freezing part of the system, but also makes the simulation more realistic in some cases. A protein system, Human Immunodeficiency Virus Type II Protease (HIV) is used for illustration here.

Input files	
`frozen.inp`	Main input file
`paramstd.dat`	Energy parameter file
`hiv.pdb`	PDB coordinate file

Output files	
`frozen.out`	Main output file

```
write verbose 3 file frozen.out title Frozen atom schemes *
create
  build primary name hiv type protein read file hiv.pdb
  read coordinates name hiv brookhaven file hiv.pdb
  build types name hiv
quit
setmodel
   setpotential
     mmechanics
   quit
   read parm file paramstd.dat noprint
   solute translate rotate diagonal
   enrg parm cutoff 20.0 -
     listupdate 100 diel 1.0 nodist print 1
   enrg cons bond
   zonecons freeze  name hiv allheavy
```

Freeze all heavy atoms in HIV complex.

```
   zonecons chain   name hiv chainname A free  chainname B fixed
```

Make chain A in HIV to be free, and chain B to be frozen.

```
   zonecons sphere  name hiv resn 20 atomname CA relax rad 10.0 buffrad 12.0
```

Relax a sphere, with the center located at residue 20 atom alpha-carbon and a radius 10A. The buffer radius is 12A, which means the atoms located in the shell between radius 10A and radius 12A is belong to the buffer region.

```
zonecons residue name hiv resn 10 backbone fixed  resn 11 sidechain free
```

Make residue 10's backbone atoms fixed, and residue 11's sidechain atoms free.

```
zonecons resseq  name hiv resn 20 to 40 buffer  resn 40 to 100 fixed
```

Put residues from 20 to 40 in the buffer region, and residues from 40 to 100 in frozen region.

```
zonecons atom    name hiv atmn 45 free  atmn 50 fixed  atmn 52 buffer
```

Make atom 45 free, atom 50 fixed, and atom 52 in buffer.

```
quit
minimize
 input cntl mxcyc 100 rmscut 0.01 deltae 1.0e-3
 steepest dx0 0.05 dxm 1.0
 run
 write pdb brookhaven name hiv file hiv_min.pdb
quit
end
```

C.2.2 Binding Energy

This example illustrates how to calculate binding energy for protein/ligand docked complex. Streptavidin/Biotin complex is used for illustration. Three separate minimizations must be run to get the binding energy: protein with ligand, protein alone, ligand alone. The binding energy can be calculated by E(bind) = E(prot+lig) - E(prot) - E(lig).

Input files	
`prot-lig.inp`	Main input file
`paramstd.dat`	Energy parameter file
`prot.pdb`	Coordinate file
`lig.pdb`	Coordinate file

Output files	
`prot-lig.out`	Main output file

Input file for the protein alone (streptavidin, 1stp).

```
write file prot.out -
   title BInding Energy of protein/ligand complex *
creat
   build primary name 1stp type protein read file prot.pdb
```

```
!  build primary name drug type ligand read file lig.pdb
   read coordinates name 1stp brookhaven file prot.pdb
!  read coordinates name drug brookhaven file lig.pdb
   build types name 1stp
quit
setmodel
   setpotential
     mmechanics
   quit
   read parm file paramstd.dat noprint
   solute translate rotate diagonal
   enrg parm cutoff 12.0 -
     listupdate 100 diel 1.0 nodist print 10
   enrg cons bond
quit
minimize
   input cntl mxcyc 5000 rmscut 0.01 deltae 1.0e-3
   steepest dx0 0.05 dxm 1.0
!  read restart coordinates formatted box file prot.min
   run
   write restart coordinates formatted box file prot.min
quit
end
```

Input file for the ligand alone (biotin). It should be pointed out that the ligand molecule must have all H atoms added (use other programs, such as ChemEdit or MacroModel, to add them). Since there is there is no template file in priori for drug molecules, the program needs to build a template file from the PDB file, which thus requires H atoms to be present in the ligand PDB file. However, proteins do not require all H atoms in hte PDB files (which means you can use PDB files from Brookhaven database), since there are templates for all residues and program will automatically match missing H atoms.

```
write file lig.out -
   title BInding Energy of protein/ligand complex *
creat
!  build primary name 1stp type protein read file prot.pdb
   build primary name drug type ligand read file lig.pdb
!  read coordinates name 1stp brookhaven file prot.pdb
   read coordinates name drug brookhaven file lig.pdb
   build types name drug
quit
setmodel
   setpotential
```

```
      mmechanics
   quit
   read parm file paramstd.dat noprint
   solute translate rotate diagonal
   enrg parm cutoff 12.0 -
     listupdate 100 diel 1.0 nodist print 10
   enrg cons bond
quit
minimize
   input cntl mxcyc 5000 rmscut 0.01 deltae 1.0e-3
   steepest dx0 0.05 dxm 1.0
!  read restart coordinates formatted box file lig.min
   run
   write restart coordinates formatted box file lig.min
quit
end
```

Input file for the protein ligand complex (streptavidin + biotin).

```
write file prot-lig.out -
   title BInding Energy of protein/ligand complex *
creat
   build primary name 1stp type protein read file prot.pdb
   build primary name drug type ligand read file lig.pdb
   read coordinates name 1stp brookhaven file prot.pdb
   read coordinates name drug brookhaven file lig.pdb
   build types name 1stp
   build types name drug
quit
setmodel
   setpotential
     mmechanics
   quit
   read parm file paramstd.dat noprint
   solute translate rotate diagonal
   enrg parm cutoff 12.0 -
     listupdate 100 diel 1.0 nodist print 10
   enrg cons bond
quit
minimize
   input cntl mxcyc 5000 rmscut 0.01 deltae 1.0e-3
   steepest dx0 0.05 dxm 1.0
!  read restart coordinates formatted box file prot-lig.min
   run
   write restart coordinates formatted box file prot-lig.min
```

```
quit
end
```

The above examples show how to calculate binding energies in gas phase. If user wants to calculate the binding energy in solvent, he can specify continuum solvation models SGB or PBF in calculation by the following modification in SETMODEL.

```
setmodel
   setpotential
!    mmechanics
     mmechanics consolv [pbf | sgb]
   quit
   read parm file paramstd.dat noprint
   solute translate rotate diagonal
   enrg parm cutoff 12.0 -
     listupdate 100 diel 1.0 nodist print 10
   enrg cons bond
quit
```

C.2.3 Protein/Water Part I. Calculating the Protein Size

This set of examples illustrates the steps required to build a protein/water system for a molecular dynamics simulation starting with only a set of protein coordinates. The first step in the process is the calculation of the size of the example protein, pancreatic trypsin inhibitor, so that the dimensions of the solvent system can be determined.

Input files	
`ptisize.inp`	Main input file
`argbnewr.dat`	Residue topology file
`alaenewr.dat`	Residue topology file
`pti4.pdb`	Coordinate file (PDB format)
`paramstd.dat`	Parameter file

Output files	
`ptisize.out`	Main output file

```
write file  ptisize.out -
      title Calculating the Size of Pancreatic Trypsin Inhibitor *
create
   build newresidue argb file argbnewr.dat -
```

```
                alae file alaenewr.dat
   build primary name pti type protein -
         read file pti4.pdb crosslink -
         substitute arg to argb rnumber 1 -
         substitute ala to alae rnumber 58
   read coordinates brookhaven name pti file pti4.pdb
   build crosslink automatic
quit
```

The `solute` subtask of `setmodel` is used to translate and rotate the protein to the origin and to align the longest axis with the z axis. The maximum dimensions of the protein will be found in the output file. When 16 Å are added to these dimensions then there will be room for approximately 3 layers of water molecules around the protein. Task `setmodel` will also report the net charge of the protein. This number will be used to determine the number of counterions necessary for the simulation system. After this input file is run two intermediate files should be run.

The first ('`fullboxmin.inp`') will generate a box of water with the full dimensions, which are determined by the output of ('`ptisize.out`'), of the final box of water and will then minimize this box for 100 steps. The second job ('`fullboxdyn.inp`') performs a molecular dynamics run for 1 psec to equilibrate this system of approximately 3000 water molecules, calculated in first run ('`fullboxmin.inp`'). The final input file is '`placepti.inp`'. This run will surround the protein and ions in a box of water molecules using the protein dimensions previously determined.

```
setmodel
   setpotential
     mmechanics
   quit
   read parm file paramstd.dat noprint
   solute translate rotate
   energy parm cutoff 8.0 listupdate 5 dielectric 1.0 nodistance
quit
end
```

The following input file, '`fullboxmin.inp`', performs the `minimize` task on the solvent system. In this run we have started from a template solvent system composed of 216 water molecules in an 18.6206 Å cube. This system is enlarged according to the protein size found in the previous calculation. In this case the enlarged solvent system of 3148 water molecules occupying a $40.7 \times 42.1 \times 54.9$ Å region is minimized and a restart file ('`fullboxmin.rst`') is written for subsequent equilibration. The output listing file for this step has been omitted.

```
!! MAINOUTPUT fullboxmin.out fullboxmin.out Main output file
```

```
!! MAININPUT  fullboxmin.inp fullboxmin.inp Main input file
!! INPUT spccon.dat spccon.dat          Constraint file
!! INPUT hoh216.xyz hoh216.xyz          Solvent coordinate file
!! INPUT paramstd.dat paramstd.dat      Parameter file
!! OUTPUT fullboxmin.rst fullboxmin.rst       Coordinates of Minimized full box
!! DESCRIPTION FILE  fullboxmin.des
!! TITLE Minimization of Full-size Box of Water Molecules for pti/water system

SET FFIELD AMBER86

WRITE file fullboxmin.out -
      title Minimization of Full-size Box of Water Molecules -
            for PTI/Water System *
CREATE
   build solvent name solvent1 type spc nmol 3148 h2o
QUIT

SETMODEL
   setpotential
      mmechanics
   quit
   energy parm cutoff 7.5 diel 1.0 nodistance listupdate 10
   energy molcutoff name solvent1
   energy constraint read file spccon.dat
   read parm file paramstd.dat noprint
! New system size (maximum pti dimensions + 16)
   solvent old file hoh216.xyz bx 40.7 by 42.1 bz 54.9
   energy periodic name solvent1 bx 40.7 by 42.1 bz 54.9
QUIT

MINM
  input cntl mxcyc 100
  conjugate dx0 0.01 dxm 1.0
  run
  write restart coordinates formatted real8 file fullboxmin.rst
QUIT
END
```

Input file '`fullboxdyn.inp`' is used to perform 1 ps of molecular dynamics on the solvent system from the previous minimization run saving a restart file for the next step. The output listing file for this step has been omitted.

```
!! MAINOUTPUT fullbox.out fullbox.out Main output file
!! MAININPUT  fullbox.inp fullbox.inp Main input file
!! INPUT  spccon.dat   spccon.dat     Constraint file
!! INPUT  paramstd.dat paramstd.dat   Parameter file
!! INPUT  fullboxmin.rst  fullboxmin.rst    Coordinates of minimized full box
!! OUTPUT fullboxdyn.rst  fullboxdyn.rst    Coordinate restart file at 298K
!! DESCRIPTION FILE    fullbox.des
!! TITLE MD Simulation on full-size box of Water Molecules for pti/water *

SET FFIELD AMBER86

WRITE file fullboxdyn.out -
      title MD Simulation on full-size box of Water Molecules for pti/water *

CREATE
   build solvent name solvent1 type spc h2o nmol 3148
QUIT

SETMODEL
   setpotential
      mmechanics
   quit
   energy parm cutoff 7.5 diel 1.0 nodist listupdate 10
   energy periodic name solvent1 bx 40.7 by 42.1 bz 54.9
   energy molcutoff name solvent1
   energy constraints read file spccon.dat
   read parm file paramstd.dat noprint
QUIT

put 1.0 into 'ttime'
put 0.0020 into 'timestep'
put 'ttime' / 'timestep' into 'nstep'
put 10.0 * 'timestep' into 'relax'

DYNAMICS
  input cntl -
       nstep 'nstep' delt 'timestep' relax 'relax' seed 100 -
       initialize temperature at 298.0 constant temperature -
       nprnt 10 tol 1.e-7
  input target temperature 298.0
  read restart coordinates formatted real8 file fullboxmin.rst
  run
```

```
  write restart coordinates formatted real8 file fullboxdyn.rst
QUIT

END
```

C.2.4 Protein/Water Part II. Placing a Protein into Water

This illustrates the final step of placing pancreatic trypsin inhibitor protein in water.

Input files	
`placepti.inp`	Main input file
`argbnewr.dat`	Residue topology file
`alaenewr.dat`	Residue topology file
`pti4.pdb`	Coordinate file (PDB format)
`paramstd.dat`	Parameter file
`pticonstr.dat`	Constraint file
`spc3148.xyz`	Coordinates of waters
`header.3148`	Header line for Coordinate file

Output files	
`placepti.out`	Main output file
`placepti.rst`	Coordinate Restart file

```
write file placepti.out -
      title Placing Pancreatic Trypsin Inhibitor into water *
create
```

Two new residues are specified for the first and last residues. These are specially capped to make them the appropriate zwitterionic forms. In this case an arginine (NH_3^+) and alanine (COO^-) are used.

```
build newresidue argb file argbnewr.dat -
              alae file alaenewr.dat
```

The sequence is taken from the protein data bank file, '`pti4.pdb`'. The first and last residues are substituted with the zwitterionic forms and the list of crosslinks are found automatically from the protein data bank file.

```
build primary name pti type protein -
      read file pti4.pdb crosslink -
      substitute arg to argb rnumber 1 -
      substitute ala to alae rnumber 58
```

The cartesian coordinates are read in from the protein data bank file and the bonds, angles and dihedrals due to crosslinks are built on the next line.

```
read coordinates brookhaven name pti file pti4.pdb
build crosslink automatic
```

A bath of 3148 SPC water molecules is made. This number is chosen to be larger than the final number of water molecules that will be present after the "full box" solvent has been replicated and extra water molecules removed (there is a bug in `IMPACT` that produces a division by zero if this number is smaller). The next line adds 6 chloride ions onto the end of the protein. These ions are not connected to the protein by bonds.

```
build solvent name solvent1 type spc nmol 3148 h2o
build primary ions name pti clm 6 end
quit
setmodel
  setpotential
    mmechanics
  quit
  read parm file paramstd.dat noprint
```

The solute (PTI) is translated to the origin and rotated so that the maximum dimension is along the z axis. The skip value means that the last 6 residues of PTI are skipped in this calculation of translation and rotation. The `mixture` option uses a density of 1.1 for the protein to calculate the number of water molecules to be removed. `Solvent old` will take its input box of 3148 water molecules ('`spc3148.xyz`') and surround the protein with water to fill the final box dimension of $40.7 \times 42.1 \times 54.9$ Å. The full box has dimensions large enough to surround the protein, and was generated using the input file '`fullboxdyn.inp`'. The coordinate file '`spc3148.xyz`' was obtained by removing the header from '`fullboxdyn.rst`' (produced by '`fullboxdyn.inp`') and appending the result to the file '`header.3148`'. The ions are placed in sites at which the protein produces the most favorable electrostatic potential (most positive, for negative chloride ions). Only water sites are tested in the potential calculations: the ions are placed one at a time in place of the water molecule that is determined to have the highest electrostatic potential. As each ion is placed it contributes to the electrostatic potential calculation for the next ion. The first `energy` line sets up a box with periodic boundary conditions and dimensions given by the parameters `bx`, `by` and `bz` in Å. The next line specifies that the species `solvent1` (the water part) will use a molecular cutoff. By default the protein has an atomic cutoff. The third `energy` line sets the cutoff and list updating

frequency, and a dielectric function of 1.0 (constant) for the electrostatic energies.

```
    solute translate rotate skip 6 name pti
    mixture density 1.10
    solvent old file spc3148.xyz bx 40.7 by 42.1 bz 54.9 -
      place charge negative 6 electrostatic cutoff 9.0 name pti
    energy periodic name solvent1 bx 40.7 by 42.1 bz 54.9
    energy molcutoff name solvent1
    energy parm cutoff 8.0 listupdate 5 diel 1.0 nodistance print 10
```

The next two lines specify `SHAKE` and `RATTLE` constraints. The first line specifies that all bonds will be constrained and that all bonds and angles involving lone pairs (on the sulfurs in this case) are constrained as well. The next line reads in a file containing an additional constraint for the water molecules (the H-H distance).

```
    energy constraint bond lonepair
    energy constraint read file pticonstr.dat
quit
```

A minimization is performed for 200 steps and then the dynamics is started.

```
minimize
 input cntl mxcyc 200
 conjugate dx0 0.01 dxm 1.0
 run
 write restart coordinates formatted real8 file placepti.rst
quit
```

The `input cntl` line specifies that 10 steps of molecular dynamics will be performed using a time step of 1 fsec (0.001 psec), a relaxation time of 10 fsec for the temperature scaling. The target temperatures are specified on the next line. The `run` command actually begins the simulation.

For real runs the dynamics will need at least 10 psec of equilibration. It should be noted that here 298K is used as the target temperature only for the purpose of illustration. In fact, a temperature jump from 0K to 298K is believed to be too abrupt and probably causes large perturbations to the system. We have performed test runs with a different heating schedule: increase the temperature from 1K to 298K in steps of about 100K, equilibrating the system for 2 psec at each temperature. The final structure was compared to that of the same total amount of equilibration (8 psec) at 298K, with no simulation at intermediate temperatures. Even with such short simulations, the structure produced by the "abrupt jump" showed more visible deviation from the starting crystal structure (‘`pti4.pdb`’), in some regions of the protein, than did the "gradual increase" structure.

The output listing for this simulation is very lengthy and is not included here.

```
dynamics
   input cntl -
        nstep 10 delta 0.00100 relax 0.0100 nprnt 1 -
        constant temperature byspecies seed 100 stop rotations -
        initialize temperature at 298.0
   input target temperature 298.0 name pti -
        temperature 298.0 name solvent1
   run
quit
end
```

C.2.5 PTI in water (9.0 Angstrom)

This illustrates a short molecular dynamics simulation of the pancreatic trypsin inhibitor protein in water. This example uses a 9 Å cutoff for non-bonded interactions.

Input files	
`pti9c.inp`	Main input file
`pti9c.inp`	Main input file
`argbnewr.dat`	Residue topology file
`alaenewr.dat`	Residue topology file
`pti4.pdb`	Coordinate file (PDB format)
`paramstd.dat`	Parameter file
`pticonstr.dat`	Constraint file
`pti1ps.rst`	Coordinates and velocities restrart file

Output files	
	Main output file
`pti9c.out`	Main output file

```
write file pti9c.out -
      title Pancreatic Trypsin Inhibitor/water Simulation -
      (9.0 Angstrom cutoff) *
create
```

Two new residues are specified for the first and last residues. These are specially capped to make them the appropriate zwitterionic forms. In this case an arginine (NH_3^+) and alanine (COO^-) are used.

```
   build newresidue argb file argbnewr.dat -
                   alae file alaenewr.dat
```

The sequence is taken from the Protein Data Bank file, '`pti4.pdb`'. The first and last residues are substituted with the zwitterionic forms and the list of crosslinks is found automatically from the protein data bank file.

```
build primary name pti type protein -
      read file pti4.pdb crosslink -
      substitute arg to argb rnumber 1 -
      substitute ala to alae rnumber 58
```

The next two lines read in the cartesian coordinates from the protein data bank file, and build the bonds, angles and dihedrals due to crosslinks.

```
read coordinates brookhaven name pti file pti4.pdb
build crosslink automatic
```

The next lines create a bath of 2943 SPC water molecules, and add six chloride ions to the solution. These ions are not connected to the protein by bonds.

```
build solvent name solvent1 type spc nmol 2943 h2o
build primary ions name pti clm 6 end
quit
setmodel
   setpotential
      mmechanics
   quit
   read parm file paramstd.dat noprint
```

The first `energy` line sets up a box with periodic boundary conditions and dimensions given by the parameters `bx`, `by` and `bz` in Å. The next line specifies that the species `solvent1` (the water part) will use a molecular cutoff. By default the protein has an atomic cutoff. The third `energy` line sets the cutoff and list updating frequency, and a dielectric function of 1.0 (constant) for the electrostatic energies.

```
energy periodic name solvent1 bx 43.2 by 46.9 bz 47.3
energy molcutoff name solvent1
energy parm cutoff 9.0 listupdate 5 diel 1.0 nodistance
```

The next two lines specify `SHAKE` and `RATTLE` constraints. The first line specifies that all bonds will be constrained and that all bonds and angles involving lone pairs (on the sulfurs in this case) are constrained as well. The next line reads in a file containing an additional constraint for the water molecules (the H-H distance).

```
energy constraint bond lonepair
energy constraint read file pticonstr.dat
quit
dynamics
```

The `input cntl` line specifies 10 steps of molecular dynamics using a time step of 1 fsec (0.001 psec) and a relaxation time of 10 fsec for the temperature scaling. The next line specifies target temperatures for each species, and

the following line reads in the initial coordinates and velocities. The `run` command actually begins the simulation.

```
    input cntl -
          nstep 10  delta 0.00100 relax 0.0100 nprnt 2 -
          constant temperature byspecies -
          seed 100
    input targ temp 298.0 name pti temp 298.0 name solvent1
    read restart coordinates and velocities formatted -
      file pti1ps.rst nobox
    run
quit
end
```

C.2.6 MD Simulation with the Ewald method

This example illustrates how to run a simulation using the Ewald summation method for the calculation of the electrostatic interactions in a fully periodic system. A simple (and small) system of about 216 water molecules is used, and a one picosecond simulation is run.

Input files	
`ewald.inp`	Main input file
`paramstd`	Energy parameter file
`tip4p.con`	Energy constraints
`tip4p.eq`	Coordinate and velocity restart file

Output files	
`ewald.out`	Main output file

```
write file ewald.out -
   title TIP4P Water MD *
```

We first create a system of 216 `TIP4P` water molecules.

```
create
   build solvent name solvent1 type tip4p nmol 216 h2o
quit
setmodel
   setpotential
```

To instruct `IMPACT` to use the Ewald summation method two things are needed: (a) all species must have periodic boundary conditions; and (b) the keyword `ewald` must follow `mmechanics`.

```
    mmechanics ewald
  quit
  read parm file paramstd noprint
   enrg parm cutoff 9.5 listupdate 10 diel 1.0 nodist
   enrg periodic name solvent1 bx 18.6353 by 18.6353 bz 18.6353
```

TIP4P must be constrained, so we read the constraint file '`tip4p.con`'. Note also that a molecular cutoff is selected for the solvent; however, when using the FMM this is completely ignored.

```
   enrg cons read file tip4p.con
   enrg molcut name solvent1
quit
dynamics
```

We use this example also as a test of energy conservation, so let's run a one picosecond simulation at constant energy.

```
input cntl -
    nstep 1000 delt 0.001 relax 0.05 taup 0.10 seed 100 stop rotations -
    constant totalenergy nprnt 50 tol 1.e-7
read restart coordinates and velocities box real8 -
  external file tip4p.eq
```

We will see later that the Fast Multipole Method works nicely together with the r-RESPA integrators. The Ewald summation, however, does not, at least for the moment, so we must use the default (Verlet) integrator and a short time step.

```
  run
quit
end
```

C.2.7 Minimization Using Varying Energy Function Weights

In this example, a conotoxin structure that was folded in a previous Monte Carlo simulation is minimized with varying weights applied to the van der Waals and NOE constraint terms of the energy function.

Input files	
`conotoxin.inp`	Main input file
`paramstd.dat`	Parameter file
`conotoxin.dat`	Coordinate file (IMPACT format)
`conotoxin.noe`	NOE constraint file

Output files	
`conotoxin.out`	Main output file
`conotoxrst1`	Coordinate restart file
`conotoxrst2`	Coordinate restart file
`conotoxrst3`	Coordinate restart file
`conotoxrst4`	Coordinate restart file
`conotoxpdb1`	Coordinate file (PDB format)
`conotoxpdb2`	Coordinate file (PDB format)
`conotoxpdb3`	Coordinate file (PDB format)
`conotoxpdb4`	Coordinate file (PDB format)

```
write file conotoxin.out -
      title Minimization using varying energy function weights *
```

Build the initial structure of the conotoxin from the coordinates in the file '`conotoxin.dat`'. Crosslink the sulfurs in the cystine residues.

```
create
  build primary name conotoxin type protein -
    glu cyx cyx asn pro ala cyx gly arg hid tyr ser cyx end
  read coordinates name conotoxin file conotoxin.dat
  build crosslinks name conotoxin -
    resnumber 2 atname sg resnumber 7 atname sg -
    resnumber 3 atname sg resnumber 13 atname sg
quit
```

Initialize one-dimensional tables to be used as counters and weighting coefficients. The integer table `'counter'` is used as the control variable for the `while` loop.

```
put 0.0001 into 'wtvdw'
put 1.0    into 'wtnoe'
put 1      into 'counter'
put 50     into 'increment'
put 'increment' into 'stepcount'
while 'counter' le 4
```

The one-dimensional character tables `'rstfile'` and `'pdbfile'` are initialized with the concatenation of constant strings and the character representation of the loop control variable, `'counter'`. The integer table `'increment'` holds the number of minimization cycles to be performed with each set of constraint weights.

```
  put $conotoxrst$ concat ( char 'counter') into 'rstfile'
  put $conotoxpdb$ concat ( char 'counter') into 'pdbfile'
```

The energy function for this iteration is initialized using `setmodel`. On each iteration, the weighting coefficients for the NOE and van der Waals constraint terms in the energy function are assigned the current values of

'wtnoe' and 'wtvdw', respectively. The NOE distance constraints are read from the file 'conotoxin.noe'.

```
setmodel
      read parm file paramstd.dat noprint
      energy parm cutoff 10.0 diel 1.0 distance listupdate 10  print 50
      setpotential
         mmechanics force noecon name conotoxin all no14 noel nohb
         constraint name conotoxin noec dist file conotoxin.noe con1 40 con2 2
         weight constraint name conotoxin noe 'wtnoe'
         weight intermolecular vdw 'wtvdw'
      quit
quit
```

The system is minimized using the conjugate gradient minimizer. The value of the table, 'increment' is used specify the number of cycles of minimization to be performed. The values of the initial and maximum step sizes as well as the convergence criteria are typical. Coordinate restart and Brookhaven PDB format files are written after minimization.

```
minm
      conjugate  dx0 0.5 dxm 1.0
      input cntl mxcyc 'increment' rmscut 0.1 deltae 0.0001
      run
      write restart coordinates formatted file 'rstfile'
      write pdb coordinates file 'pdbfile' name conotoxin
quit
```

The Lennard-Jones 6-12 component of the system energy is appended to the table 'energylj612', and the number minimization cycles is appended to the table 'mincycles'.

```
   put 'energylj612' append 'current.lj612' into 'energylj612'
   put 'mincycles' append 'stepcount' into 'mincycles'
```

The values are weighting coefficients are scaled, the loop control variable is incremented, and the minimization step count is updated.

```
   put 'wtvdw' * 10.0  into 'wtvdw'
   put 'wtnoe' *  2.0  into 'wtnoe'
   put 'stepcount' + 'increment' into 'stepcount'
   put 'counter' + 1   into 'counter'
   reset 'current.lj612'
endwhile
```

The result tables 'mincycles' and 'energylj612' are printed in the output file.

```
table
   printoptions -
     title Minimization cycles versus 6-12 energy  *
```

```
   print 'mincycles' 'energylj612'
quit
end
```

C.2.8 Calculation of Some Energetic Quantities of a Helical Protein

This example illustrates a variety of the capabilities of the `analysis` task for calculating selected energetic quantities.

Input files	
`analener.inp`	Main input file
`paramstd.dat`	Standard energy parameter file

Output files	
`analener.out`	Main output file

```
write file analener.out -
     title Calculation of Some Energetic Quantities of a Helical Protein *
```

Use task `create` to build the example helical protein structure.

```
create
  build primary name mol1 type protein ala ala cys ala end
  build secondary name mol1 helix fres 1 lres 4
quit
```

Subtask `setmodel` sets up the energy function before any `analysis` subtasks that calculate energetic quantities are performed.

```
setmodel
   setpotential
      mmechanics
   quit
   read parm file paramstd.dat noprint
   energy parm cutoff 8.0 diel 1.0 dist
quit
```

Subtask `energy` calculates all terms in the current energy function.

```
analysis
  energy allterms
quit
```

Calculate the hydrogen bonding energy with a distance cutoff of 8 Å and an angular cutoff of 90 degrees.

```
analysis
   energy analyze hbond hbond hbcut 8.0 hbangcut 90.0
quit
```

Calculate the energy components between all residues of species *mol1*.

```
analysis
  energy res-res one name mol1 allterms
quit
end
```

C.2.9 Calculation of Some Structural Features of a Helical Protein

This example illustrates a variety of the capabilities of the `analysis` task for calculating geometrical features of proteins.

Input files	
`analgeo.inp`	Main input file

Output files	
`analgeo.out`	Main output file
`noeconstr.out`	Simulated NOE constraints

```
write file analgeo.out -
      title Calculation of Some Structural Features of a Helical Protein *
```

Use task `create` to build the example helical protein structure.

```
create
  build primary name mol1 type protein ala ala cys ala end
  build secondary name mol1 helix fresidue 1 lresidue 4
quit
analysis
```

Subtask `measure` is used to calculate selected bond distances, bond angles, and torsion angles.

```
 measure name mol1
  calc bond resnumber 1 atomname ca resnumber 2 atomname ca -
       angl resnumber 1 atomname c  resnumber 1 atomname o -
       resnumber 3  atomname hn -
       tors resnumber 1 atomname ca resnumber 1 atomname c -
       resnumber 2  atomname n resnumber 2 atomname ca
 quit
```

Here, subtask `measure` is used to calculate geometrical features of the side chain on residue three.

```
measure name mol1
 calc side resnumber 3
quit
```

Subtask `NOE` is used to generate all interresidue distances between hydrogen atoms in the 1.5 to 4.5 Å range. A constraint file, '`noeconstr.out`', is also generated using distance tolerances of 0.5 Å.

```
noe name mol1 ucut 4.5 lcut 1.5  gen file noeconstr.out prokiral -
            plus 0.5 minus 0.5
```

Subtask `hbond` calculates the distances between H-bonding donor and acceptor atoms in the distance range of 1.5 to 4.0 Å.

```
hbond name mol1 ucut 4.0 lcut 1.5
```

Subtask `surface` calculates the solvent accesible surface area of the protein using the default resolution of 0.25 Å.

```
surface name mol1
quit
end
```

C.3 Analysis Examples

C.3.1 Structural Comparison using RMS deviations

The example illustrates the use of the `analysis` subtask `RMS` to compare two structural units in terms of their RMS deviation.

Input files	
`rms.inp`	Main input file
`rmsdata1.pdb`	Coordinate data file (PDB format)
`rmsdata2.pdb`	Coordinate data file (PDB format)
`rmsdata3.pdb`	Coordinate data file (PDB format)

Output files	
`rms.out`	Main output file

```
write file rms.out title RMS Structural Comparison *
```

Build the primary structure of the protein for this example.

```
create
  build primary name mol1 type prot ile pro gly ala thr end
quit
```

Calculate the RMS deviation between corresponding atoms of the internal structure *mol1* generated by task `create` and the coordinates stored in the Brookhaven PDB format file, '`rmsdata1.pdb`'.

```
analysis
  rms name mol1 -
     name mol1dat pdb2 file rmsdata1.pdb comp same
quit
```

Calculate the RMS deviation between the coordinates of corresponding atoms contained in the files `rmsdata2.pdb` and `rmsdata3.pdb`.

```
analysis
  rms name data1 pdb1 file rmsdata2.pdb -
      name data2 pdb2 file rmsdata3.pdb comp all
quit
end
```

C.3.2 Building a Two-Dimensional Torsion Map

This example illustrates the construction of two dimensional energy contour maps resulting from the rotation of the phi and psi angles in the alanine dipeptide.

Input files	
`torsionmap.inp`	Main input file
`paramstd.dat`	Parameter file

Output files	
`torsionmap.out`	Main output file
`tordata.meta`	Torsion map plot file(Meta format)
`potential.ps`	Potential Energy Map
`torsional.ps`	Torsional Energy Map
`lj.ps`	Lennard-Jones Energy Map
`electrost.ps`	Electrostatic Energy Map
`hbond.ps`	Hydrogen Bonding Energy Map

```
write file torsionmap.out -
title Building a Two Dimensional Torsion Map *
```

Build the primary structure of the alanine dipeptide:

```
create
build newres nma file nma
build primary name dip type prot -
  ace ala nma end
quit
```

Set up the energy functions:

```
setmodel
setpotential
  mmechanics
quit
read parm file paramstd.dat noprint
enrg parm cutoff 7.5 diel 1.0 dist
quit
```

Select torsion angles phi and psi to be varied, and select the range of variation from -180 to 180 degrees in increments of 10 degrees. Save the energy components calculated at each point in the variation in the file '`tordata.meta`' for subsequent plotting. Data in '`tordata.meta`' is formatted in five sections corresponding to five energy components, with each section being composed

of blocks of energy values for the angles varied in the order: tor1='init' through 'final', tor2='init'; tor1='init' through 'final', tor2='init+incr';... tor1='init' through 'final', tor2='final'.

To obtain meaningful plots it is best to generate the data first, examine the energy values in '`tordata.meta`' to determine what contour values should be plotted, and then use a plotting routine to produce the contour plots.

```
analysis
tormap 2d name dip -
  tor1 res 2 main 1 init -180.0 final 180.0 incr 10* -
  tor2 res 2 main 2 init -180.0 final 180.0 incr 10* -
plot delay file tordata.meta
quit
```

The following sections demonstrate the use of `IMPACT` to produce contour plots in postscript format. Each plot is written to a separate postscript file. Alternately, the ASCII data file '`tordata.meta`' could be used as input to external plotting programs.

Plot the total potential energy contour map in postscript mode.

```
plot
read 2d file tordata.meta number 1
plot file potential.ps -
  title Potential Energy Map for Ala Dip * -
  xlabel Phi * ylabel Psi * postscript -
  xmin -180.0 xmax 180.0 ymin -180.0 ymax 180.0 -
  contour 30 at -1 -2 -3 -4 -5 -6 -7 -8 -9 -10 -
              -11 -12 -13 -14 -15 -16 -17 -18 -19 -20 -
              -21 -22 -23 -24 -25 -26 -27 -28 -29 -30
quit
```

Plot the torsional energy contour map in postscript mode.

```
plot
read 2d file tordata.meta number 2
plot file torsional.ps -
          title Torsional Energy Map for Ala Dip * -
  xlabel Phi * ylabel Psi * postscript -
  xmin -180.0 xmax 180.0 ymin -180.0 ymax 180.0 -
  contour 7 at 14.0 15.0 16.0 17.0 18.0 19.0 20.0
quit
```

Plot the Lennard-Jones energy contour map in postscript mode.

```
plot
read 2d file tordata.meta number 3
plot file lj.ps -
          title Lennard-Jones Energy Map for Ala Dip * -
  xlabel Phi * ylabel Psi * postscript -
  xmin -180.0 xmax 180.0 ymin -180.0 ymax 180.0 -
```

```
  contour 12 at 2 4 6 8 10 12 14 16 18 20 -
             -1 -2
quit
```

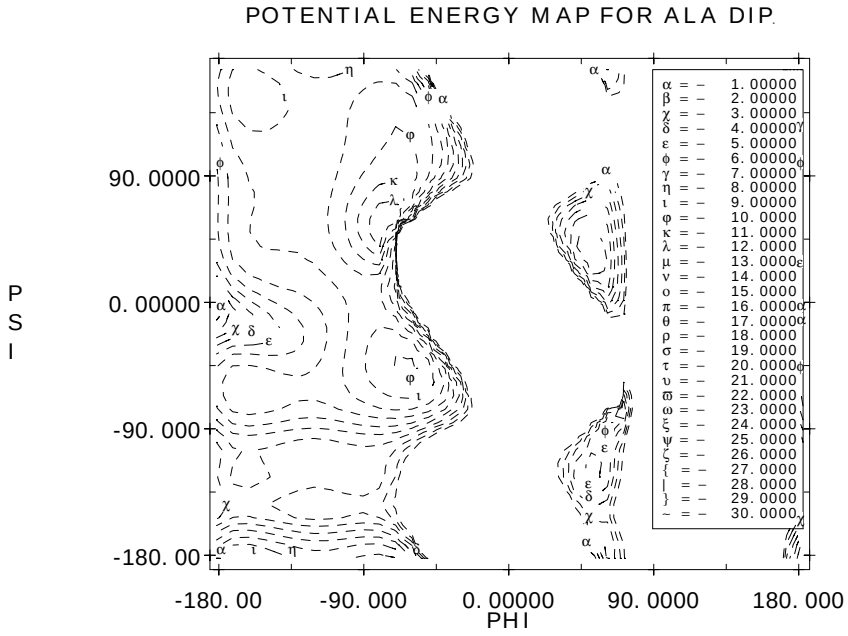
Plot the electrostatic energy contour map in postscript mode.

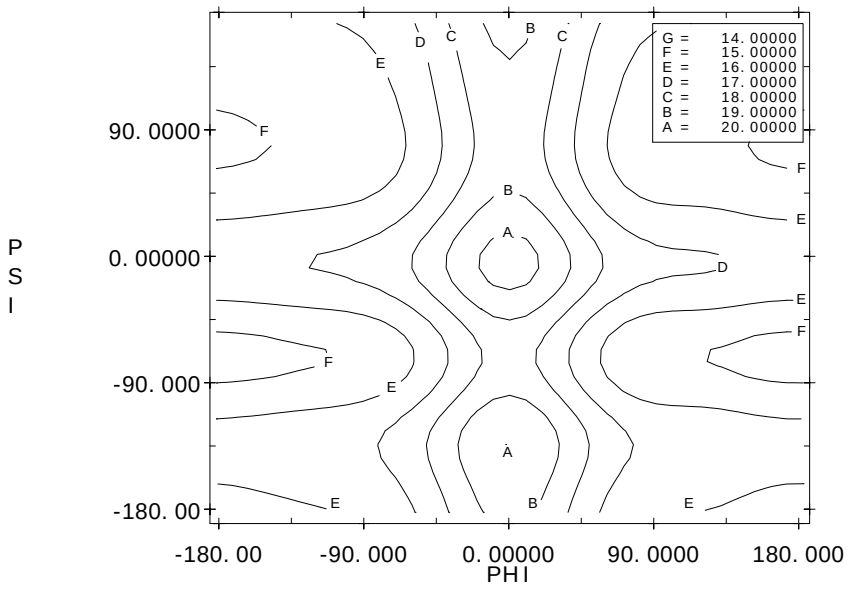
```
plot
read 2d file tordata.meta number 4
plot file electrost.ps -
          title Electrostatic Energy Map for Ala Dip * -
  xlabel Phi * ylabel Psi * postscript -
  xmin -180.0 xmax 180.0 ymin -180.0 ymax 180.0 -
  contour 16 at -15 -16 -17 -18 -19 -20 -21 -22 -23 -
             -24 -25 -26 -27 -28 -29 -30
quit
```

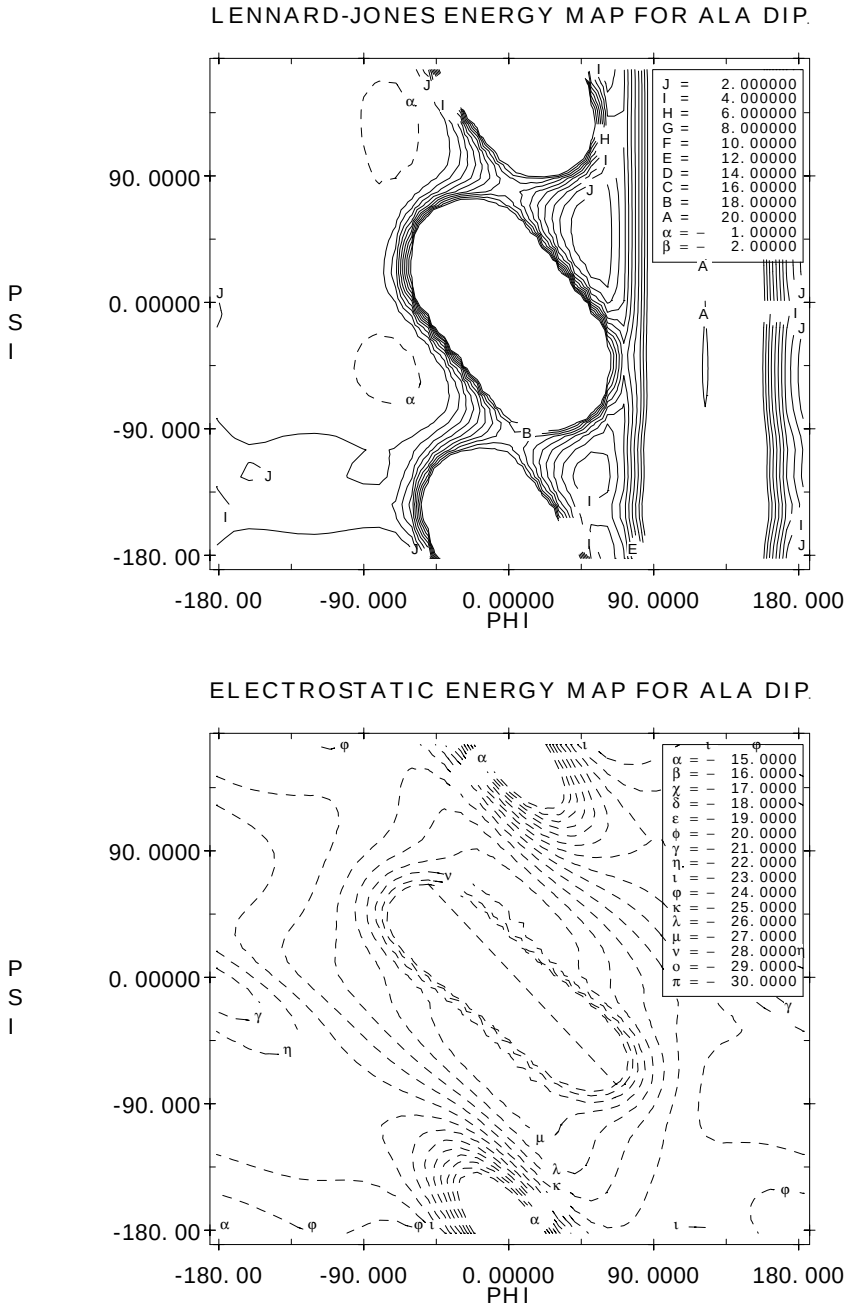
Plot the hydrogen bonding energy contour map in postscript mode.

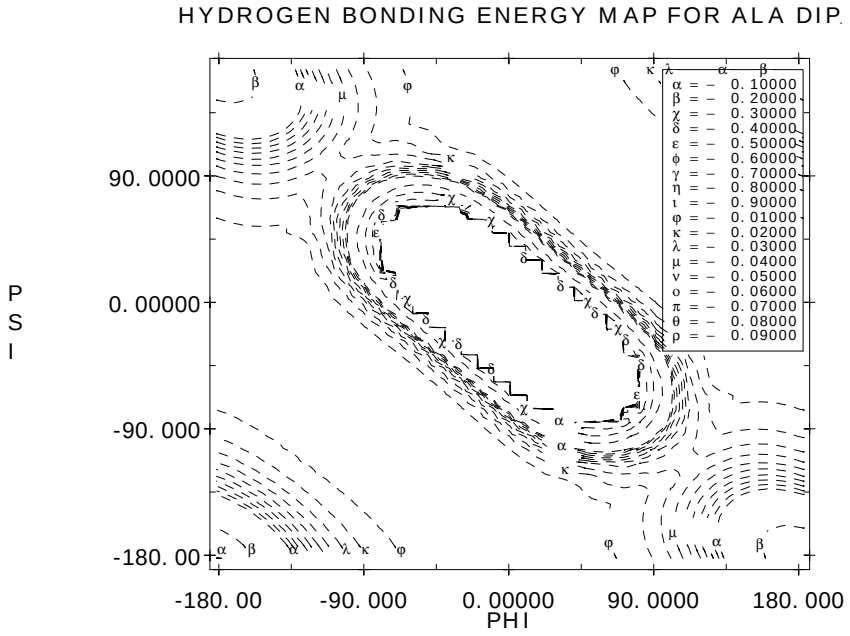
```
plot
read 2d file tordata.meta number 5
plot file hbond.ps -
          title Hydrogen Bonding Energy Map for Ala Dip * -
  xlabel Phi * ylabel Psi * postscript -
  xmin -180.0 xmax 180.0 ymin -180.0 ymax 180.0 -
  contour 18 at -0.1 -0.2 -0.3 -0.4 -0.5 -0.6 -0.7 -
             -0.8 -0.9 -0.01 -0.02 -0.03 -0.04 -0.05 -0.06 -
             -0.07 -0.08 -0.09
quit
end
```

The postscript figures from graphics files '`potential.ps`', '`torsional.ps`', '`lj.ps`', '`electrost.ps`', and '`hbond.ps`' follow:


POTENTIAL ENERGY MAP FOR ALA DIP
PSI
90. 0000
0. 00000
-90. 000
-180. 00
-180. 00
-90. 000
0. 00000
90. 0000
180. 000
PHI
α = – 1. 00000
β = – 2. 00000
γ = – 3. 00000
δ = – 4. 00000
ε = – 5. 00000
φ = – 6. 00000
γ = – 7. 00000
η = – 8. 00000
ι = – 9. 00000
φ = – 10. 0000
κ = – 11. 0000
λ = – 12. 0000
μ = – 13. 0000
ν = – 14. 0000
ο = – 15. 0000
π = – 16. 0000
θ = – 17. 0000
ρ = – 18. 0000
σ = – 19. 0000
τ = – 20. 0000
υ = – 21. 0000
ϖ = – 22. 0000
ω = – 23. 0000
ξ = – 24. 0000
ψ = – 25. 0000
ζ = – 26. 0000
{ = – 27. 0000
| = – 28. 0000
} = – 29. 0000
~ = – 30. 0000


TORSIONAL ENERGY MAP FOR ALA DIP
PSI
90. 0000
0. 00000
-90. 000
-180. 00
-180. 00
-90. 000
0. 00000
90. 0000
180. 000
PHI
G = 14. 00000
F = 15. 00000
E = 16. 00000
D = 17. 00000
C = 18. 00000
B = 19. 00000
A = 20. 00000


LENNARD-JONES ENERGY MAP FOR ALA DIP
J = 2. 000000
I = 4. 000000
H = 6. 000000
G = 8. 000000
F = 10. 00000
E = 12. 00000
D = 14. 00000
C = 16. 00000
B = 18. 00000
A = 20. 00000
α = – 1. 00000
β = – 2. 00000
90. 0000
0. 00000
-90. 000
-180. 00
PSI
-180. 00
-90. 000
0. 00000
90. 0000
180. 000
PHI
ELECTROSTATIC ENERGY MAP FOR ALA DIP
α = – 15. 0000
β = – 16. 0000
χ = – 17. 0000
δ = – 18. 0000
ε = – 19. 0000
φ = – 20. 0000
γ = – 21. 0000
η = – 22. 0000
ι = – 23. 0000
φ = – 24. 0000
κ = – 25. 0000
λ = – 26. 0000
μ = – 27. 0000
ν = – 28. 0000
ο = – 29. 0000
π = – 30. 0000
90. 0000
0. 00000
-90. 000
-180. 00
PSI
-180. 00
-90. 000
0. 00000
90. 0000
180. 000
PHI



C.3.3 Electrostatic Potential and Hydration Energy Differences

This example illustrates the analysis of molecular dynamics trajectories by two different tasks, `analysis` and `table`. It also illustrates how to generate files containing plotting data in a simple tabular form that can be processed later with your favorite graphing program.

- `Analysis` calculates the electrostatic field produced by the solute (in this example the formaldehyde molecule).
- The `potfield` subtask is used to find the electrostatic potential.
- `Plot` functions are then used to display two-dimensional contours of the potential in the output file.
- `Table` calculates the differences in solvation between the ground and excited states of formaldehyde for this formaldehyde/water system over the course of a series of trajectories.
- Using the `dynamics` task the evolution of the excited state formaldehyde using a set of atomic charges for the singlet A_2 excited state of formaldehyde.
- `Starttrack/stoptrack` begins a loop where frames of a trajectory are read sequentially. This example illustrates the use of `DICE` functions inside of this type of loop. For each frame of the trajectory the hydration

energies of formaldehyde with both excited and and ground state charges are accumulated in tables for subsequent display.

Input files	
`formh2o.inp`	Main input file
`formh2o.rst`	Initial Coordinate and velocity restart file
`gscharge.dat`	Ground state charges
`excharge.dat`	Excited state charges
`h2cordb.dat`	Residue topology file
`h2coprm.dat`	Parameter file

Output files	
`formh2o.out`	Main output file
`formh2o.trj`	Coordinate and velocity trajectory file
`formh2ogs.ps`	Ground State solvation energy plot (Postscript)
`formh2oex.ps`	Excited State solvation energy plot (Postscript)
`formh2odif.ps`	Solvation energy difference plot (Postscript)

```
write file formh2o.out -
   title H2CO Electrostatic Potential (1A1 H2CO) and Hydration (A1/A2 H2CO) *
```

Task `create` is used to build the initial coordinates for the formaldehyde water system.

```
create
   build newresidue fmd file h2cordb.dat
   build primary name formaldehyde fmd end
   build solvent name solvent1 type spc nmol 209 h2o
quit
```

Task `setmodel` initializes the energy function for the system. The energy function parameters are read from a file, '`h2coprm.dat`' in this example. Periodic boundary conditions are applied to all nonbonded solvent-solvent and solute-solvent interactions.

```
setmodel
   setpotential
      mmechanics
   quit
   read parm file h2coprm.dat noprint
   energy parm cutoff 7.5 listupdate 1 diel 1.0 nodist
   energy molcutoff name solvent1
   energy periodic name solvent1 bx 18.6206 by 18.6206 bz 18.6206
```

The charges for the ground and excited states of formaldehyde are read from the two files '`gscharge.dat`' and '`excharge.dat`', respectively. The two sets of charges are also stored in the two charge tables '`gscharge`' and '`excharge`'.

```
    read charge file excharge.dat
    put 'charge' with species:1: into 'excharge'
    reset 'charge'
    read charge file gscharge.dat
    put 'charge' with species:1: into 'gscharge'
quit
```

The `analysis` subtask `potfield` calculates the electrostatic potential due the formaldehyde in the 4 Å cube about centered at the formaldehyde carbon atom.

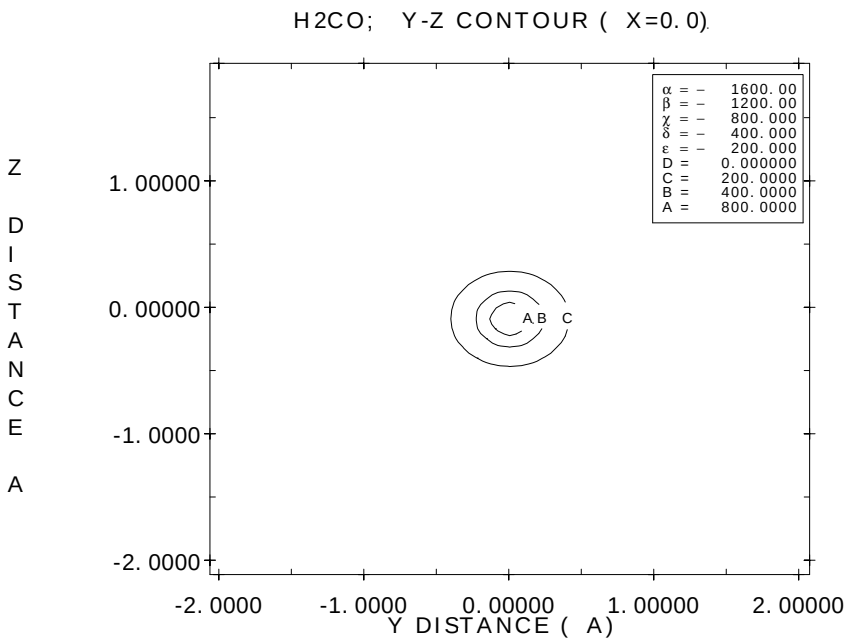
```
analysis
  potfield
    grid center name formaldehyde resn 1 atna fmc -
         boxsiz 4.0 stepsiz 0.08 chgcut 10.0
    include name formaldehyde
    run
    analysis
```

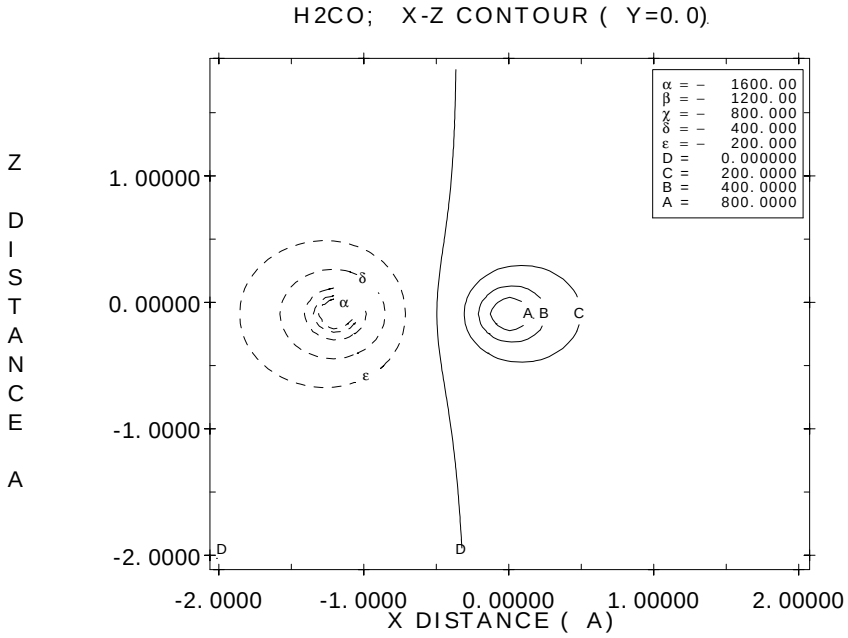
The following set of commands construct two-dimensional contour plots on several planes on interest. The locations of the planes are identified by plot title strings.

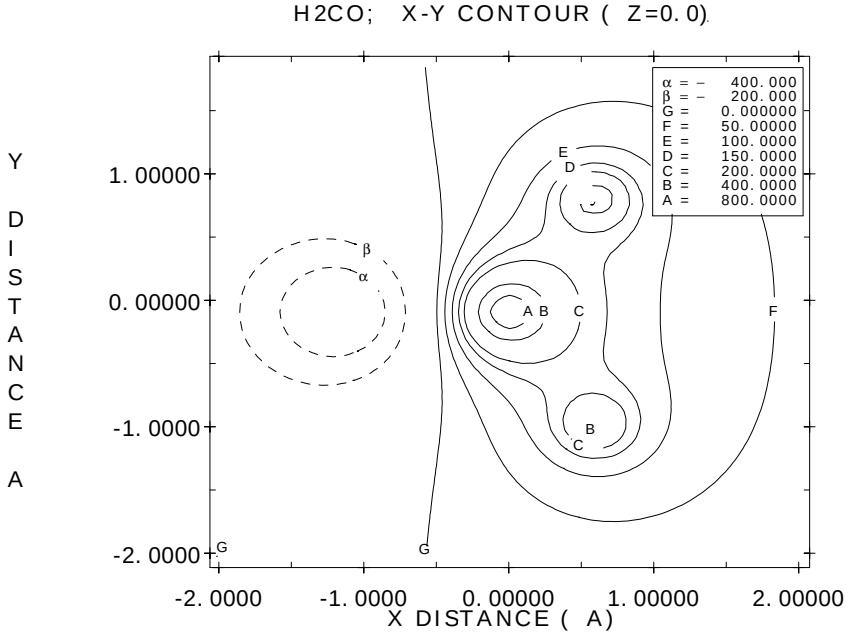
```
  plot epot make x = 0.0 -
    title  h2co; y-z contour (x=0.0) * -
    xlabel y distance (a) * -
    ylabel z distance  a * -
    contour 9 at -1600.0  -1200.0  -800.0 -400.0 -200.0 0.0 -
    200.0 400.0 800.0 -
    postscript file cont1.ps
  plot epot make y = 0.0 -
    title  h2co; x-z contour (y=0.0) * -
    xlabel x distance (a) * -
    ylabel z distance  a * -
    contour 9 at -1600.0  -1200.0  -800.0 -400.0 -200.0 -
         0.0 200.0 400.0 800.0 -
    postscript file cont2.ps
  plot epot make z = 0.0 -
    title  h2co; x-y contour (z=0.0) * -
    xlabel x distance (a) * -
    ylabel y distance  a * -
    contour 9 at -400.0 -200.0 0.0 50.0 100.0 150.0 200.0 400.0 800.0 -
    postscript file cont3.ps
```

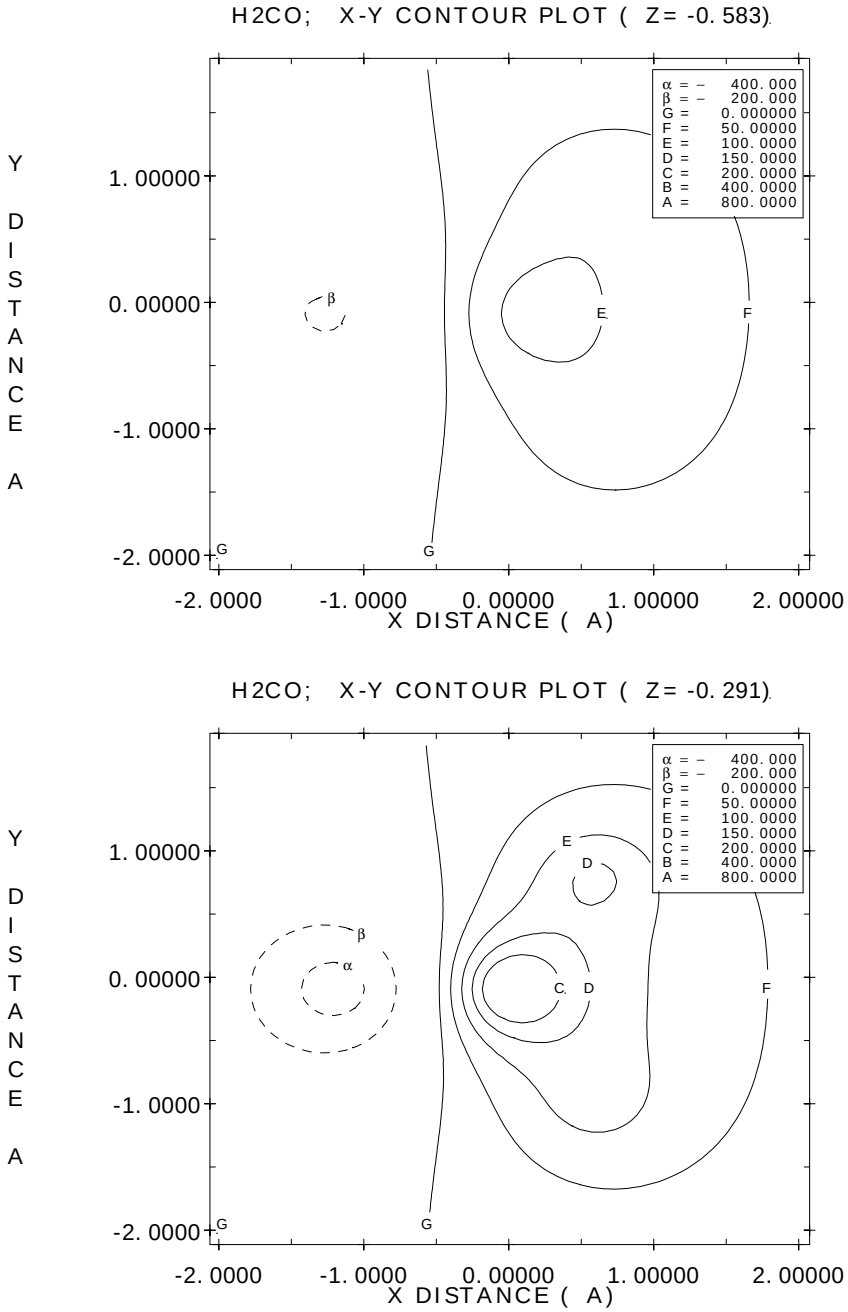
```
        plot epot make z = -0.583 -
          title  h2co; x-y contour plot (z= -0.583) * -
          xlabel x distance (a) * -
          ylabel y distance  a * -
          contour 9 at -400.0 -200.0 0.0 50.0 100.0 150.0 200.0 400.0 800.0 -
          postscript file cont4.ps
        plot epot make z = -0.291 -
          title  h2co; x-y contour plot (z= -0.291) * -
          xlabel x distance (a) * -
          ylabel y distance  a * -
          contour 9 at -400.0 -200.0 0.0 50.0 100.0 150.0 200.0 400.0 800.0 -
          postscript file cont5.ps
    quit
quit
```

The plots just generated ('`cont1.ps`' to '`cont5.ps`') are shown below:




H2CO; X-Z CONTOUR (Y=0.0)
α = – 1600.00
β = – 1200.00
χ = – 800.000
δ = – 400.000
ε = – 200.000
D = 0.000000
C = 200.0000
B = 400.0000
A = 800.0000
Z DISTANCE A
1.00000
0.00000
-1.0000
-2.0000
-2.0000
-1.0000
0.00000
1.00000
2.00000
X DISTANCE (A)


H2CO; X-Y CONTOUR (Z=0.0)
α = – 400.000
β = – 200.000
G = 0.000000
F = 50.00000
E = 100.0000
D = 150.0000
C = 200.0000
B = 400.0000
A = 800.0000
Y DISTANCE A
1.00000
0.00000
-1.0000
-2.0000
-2.0000
-1.0000
0.00000
1.00000
2.00000
X DISTANCE (A)



A variety of one dimensional tables are initialized with the parameters for the following molecular dynamics simulation. The time step in the simulation is assigned to '`dt`', the duration of the simulation in picoseconds is assigned to

'`ttime`', and the frequency with which to save trajectory frames is assigned to '`ever`'. The number of times steps and the number of trajectory records in this simulation are calculated and stored in the tables '`mstep`' and '`mrec`', respectively.

```
put 0.001 into 'dt'                                ! timestep
put 0.25  into 'ttime'     ! simulation time
put 5     into 'ever'                              ! how often traj's written
put 'ttime' div 'dt'   into 'mstep'                ! no. of dynamics steps
put 'mstep' div 'ever' into 'mrec'                 ! no. of traj's written
```

Prior to beginning the simulation, the internal charge array is updated with the formaldehyde charges for the excited state stored in table '`excharge`'. The molecular dynamics simulation is performed starting from the coordinates and velocities stored in the restart file named '`formh2o.rst`', and saving the trajectory frames in file '`formh2o.trj`'.

```
restore charge 'excharge'
dynamics
  input cntl -
      nstep 'mstep' delt 'dt' relax 0.01  -
      stop rotations -
      initialize temperature at 298.0 seed  100 -
      constant temperature byspecies -
      nprnt 100  tol 1.e-7
  input target temperature 298.0 name formaldehyde
  input target temperature 298.0 name solvent1
  read restart coordinates and velocities formatted file formh2o.rst
  write trajectory coordinates and velocities -
        external real8 file formh2o.trj every 'ever'
  run
quit
```

The one dimensional table '`tstep`' is initialized with the time between sequential trajectories, and '`tcount`' is initialized and will be used to hold the running time value. The `table` subtask `traj` is then used to specify the parameters of the trajectories stored in the trajectory file '`formh2o.trj`'. This subtask also defines which trajectories will be selected by the automatic trajectory selection subtask, `startrack`. In this example all of the trajectory frames will be selected. All tasks in the input file between the declarations of `starttrack` and `stoptrack` will be executed for each of these trajectory frames.

```
put 'dt' * 'ever' into 'tstep'
put 0 into 'tcount'
table
   traj nfile 1 maxrec 'mrec' nskip 1 delt 'dt' -
      coordinates and velocities every 'ever' traj fnames -
```

```
      external file formh2o.trj
   starttrack
quit
```

The internal charge array is updated with formaldehyde ground state charges, and the hydration energy for formaldehyde is calculated and stored in the table '`hydout`'. The sum of the atomic hydration energies is stored in table '`esolvgs`'.

```
   restore charge 'gscharge'
table
      reset 'hydration'
quit
analysis
      energy solvation of name formaldehyde by name solvent1 echooff
quit
   put 'hydration' with species:formaldehyde:atoms:*: into 'hydout'
   put sum 'hydout' into 'esolvgs'
```

The internal charge array is updated with formaldehyde excited state charges, and the hydration energy for formaldehyde is calculated and stored in the table '`hydout`'. The sum of the atomic hydration energies is stored in table '`esolvex`'. The hydration energy tables '`esolvgs`' and '`esolvex`' have three subfields. In this example, only the first subfield corresponding to the total hydration energy is of interest.

```
   restore charge 'excharge'
table
      reset 'hydration'
quit
analysis
      energy solvation of name formaldehyde by name solvent1 echooff
quit
   put 'hydration' with species:formaldehyde:atoms:*: into 'hydout'
   put sum 'hydout' into 'esolvex'
```

The total solvation energies for the ground and excited states are appended to tables '`gstable`' and '`extable`'. The total solvation energy difference is stored in the table named '`diftable`'. The time corresponding to the current trajectory is stored in table '`timelist`'. At the end of this trajectory cycle, the running time variable is updated.

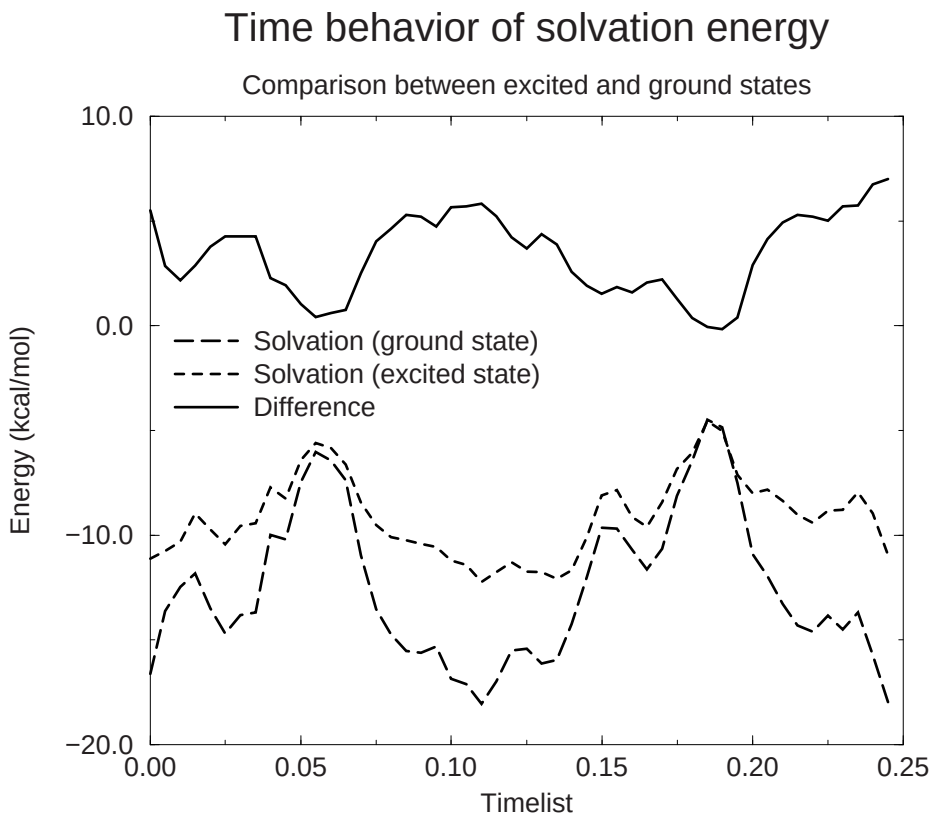
```
   put 'timelist'  append 'tcount'    into 'timelist'
   put 'gstable'   append 'esolvgs_1'   into 'gstable'
   put 'extable'   append 'esolvex_1'   into 'extable'
   put 'esolvex_1' - 'esolvgs_1' into 'diff'
   put 'diftable'  append 'diff'    into 'diftable'
   put 'tstep'  + 'tcount' into 'tcount'
table
```

```
    stoptrack
quit
```

The resulting tables are printed in tabular form in the output file, and are also written in tabular form to the files '`formh2ogs.gr`', '`formh2oex.gr`' and '`formh2odif.gr`'. The latter can be processed by a program such as Gnuplot[1] or Grace[2]. The plot below combines the three data tables; the legends were added outside of `Impact`.

```
table
  printoptions title Ground state solvation energies *
  show 'timelist' 'gstable'
  printoptions title Excited state solvation energies *
  show 'timelist' 'extable'
  printoptions title Solvation energy differences (ex-gs) *
  show 'timelist' 'diftable'
  plot 'timelist' 'gstable' tabular file formh2ogs.gr -
         xmin 0.0 xmax 'ttime' ymin -25.0 ymax 0.0 ylabel gs esolv *
  plot 'timelist'  'extable' tabular file formh2oex.gr -
         xmin 0.0 xmax 'ttime' ymin -25.0 ymax 0.0 ylabel ex esolv *
  plot 'timelist' 'diftable' tabular file formh2odif.gr -
         xmin 0.0 xmax 'ttime' ymin 0.0 ymax 10.0 ylabel ediff *
quit
end
```

[1] http://www.gnuplot.info
[2] http://plasma-gate.weizmann.ac.il/Grace/



C.3.4 Molecular Dynamics Analysis (NVE Ensemble)

This example illustrates many of the features of the `mdanalysis` task for a glycine/water simulation.

Input files	
`glyh2o.inp`	Main input file
`egly.dat`	Glycine residue data file (ext. atom)
`glyparam.dat`	Parmeter file
`spcconst.dat`	Constraint file
`glyh2o.rst`	Coordinate and velocity restart file

Output files	
glyh2o.out	Main output file
glyh2o.trj	Coordinate and velocity trajectory file
rdfN-HW1.gr	RDF data for N-HW1 in tabular format
rdfN-HW1i.gr	Integral of the previous one
rdfN-OW.gr	RDF data for N-OW in tabular format
rdfN-OWi.gr	Integral of the previous one
rdfCA-HW1.gr	RDF data for CA-HW1 in tabular format
rdfCA-HW1i.gr	Integral of the previous one
rdfCA-OW.gr	RDF data for CA-OW in tabular format
rdfCA-OWi.gr	Integral of the previous one
rdfC-HW1.gr	RDF data for C-HW1 in tabular format
rdfC-HW1i.gr	Integral of the previous one
rdfC-OW.gr	RDF data for C-OW in tabular format
rdfC-OWi.gr	Integral of the previous one
rdfO1-HW1.gr	RDF data for O1-HW1 in tabular format
rdfO1-HW1i.gr	Integral of the previous one
rdfO1-OW.gr	RDF data for O1-OW in tabular format
rdfO1-OWi.gr	Integral of the previous one
rdfOH-HW1.gr	RDF data for OH-HW1 in tabular format
rdfOH-HW1i.gr	Integral of the previous one
rdfOH-OW.gr	RDF data for OH-OW in tabular format
rdfOH-OWi.gr	Integral of the previous one
bedN-P.gr	Binding energy distribution for N
bedCA-P.gr	Binding energy distribution for CA
bedC-P.gr	Binding energy distribution for C
bedO1-P.gr	Binding energy distribution for O1
bedOH-P.gr	Binding energy distribution for OH
vcf.gr	Velocity autocorrelation function
spec.gr	Fourier spectrum of the previous one

```
set FFIELD AMBER86
write file glyh2o.out -
      title Molecular Dynamics Analysis  *
```

Task `create` is used to build the glycine water system. In this example an extended atom model of glycine is used. The residue topology for this glycine model is stored in file '`egly.dat`'.

```
create
  build newresidue egl file egly.dat
  build primary name glycine type other egl end
  build solvent name solvent1 type spc nmol 207 h2o
  print ic name glycine bond angle tors
  print structure name glycine bond angle torsion excl
```

```
  print tree name glycine
quit
```

The energy function is initialized with task `setmodel`. In this simulation a molecular cutoff will be used for nonbonded interactions for the solvent. Periodic boundary conditions are applied to nonbonded interactions between solvent molecules and between the solvent and glycine.

```
setmodel
  setpotential
    mmechanics ewald
  quit
  read parm file glyparam.dat noprint
  energy parm listupdate 1 diel 1.0 nodist
  energy periodic name glycine bx 18.6206 by 18.6206 bz 18.6206
  energy periodic name solvent1 bx 18.6206 by 18.6206 bz 18.6206
  energy constraint read file spcconst.dat
  energy molcutoff name solvent1
quit
```

The molecular dynamics simulation is run for 4 ps at constant total energy, using the r-RESPA integrator. The coordinates and velocities are stored on every cycle in the trajectory file '`glyh2o.trj`'

```
dynamics
  input cntl -
  nstep 2000 delt 0.002 relax 0.01  seed 100 -
  cons totalenergy nprnt 50 tol 1.e-7
  read restart coordinates and velocity formatted file glyh2o.rst
  write trajectory coordinates and velocities every 1 -
    external file glyh2o.trj
  run rrespa fast 3
quit
```

Task `mdanalysis` is used to calculate the radial distribution function and binding energy distribution function between selected glycine atoms and solvent atoms, treating the solvent protons as equivalent atoms. The calculation is performed using the coordinates stored in the single trajectory file '`glyh2o.trj`'. The details of the simulation are specified in the `input` subtask in the same manner as in the `dynamics` task. Note that we must specify several files to obtain all the data in tabular format; this is for two reasons: (a) the radial distribution functions (as well as the binding energy distributions) are computed for all atoms in the solute, against all atoms in the solvent molecule; and (b) for each rdf the corresponding integral is also computed. All these files are written in tabular format, for later processing with your favorite graphing package.

```
mdanalysis
   input trajectories nfiles 1 external fnames file glyh2o.trj -
```

```
    coordinates and velocities every 1 maxrec 2000 nskip 1 nobox delt 0.001 -
    rlow 0.0 rup 7.5 ngridr 100 -
    elow -100.0 eup 100.0 ngride 100 dw 1.0
  static rdf iatom name glycine ires all atomnames  n ca c o1 oh end -
             jatom name solvent1 atomnames  hw1 hw2 ow end -
                  equivalent hw1 hw2 end
  static rdf run plrdf plbed wrrdf wrbed tabular -
       file "rdfN-HW1.gr"  file "rdfN-HW1i.gr" -
       file "rdfN-OW.gr"   file "rdfN-OWi.gr" -
       file "rdfCA-HW1.gr" file "rdfCA-HW1i.gr" -
       file "rdfCA-OW.gr"  file "rdfCA-OWi.gr" -
       file "rdfC-HW1.gr"  file "rdfC-HW1i.gr" -
       file "rdfC-OW.gr"   file "rdfC-OWi.gr" -
       file "rdfO1-HW1.gr" file "rdfO1-HW1i.gr" -
       file "rdfO1-OW.gr"  file "rdfO1-OWi.gr" -
       file "rdfOH-HW1.gr" file "rdfOH-HW1i.gr" -
       file "rdfOH-OW.gr"  file "rdfOH-OWi.gr" -
       file "bedN-P.gr"    file "bedCA-P.gr" -
       file "bedC-P.gr"    file "bedO1-P.gr" -
       file "bedOH-P.gr"
  file close
quit
```

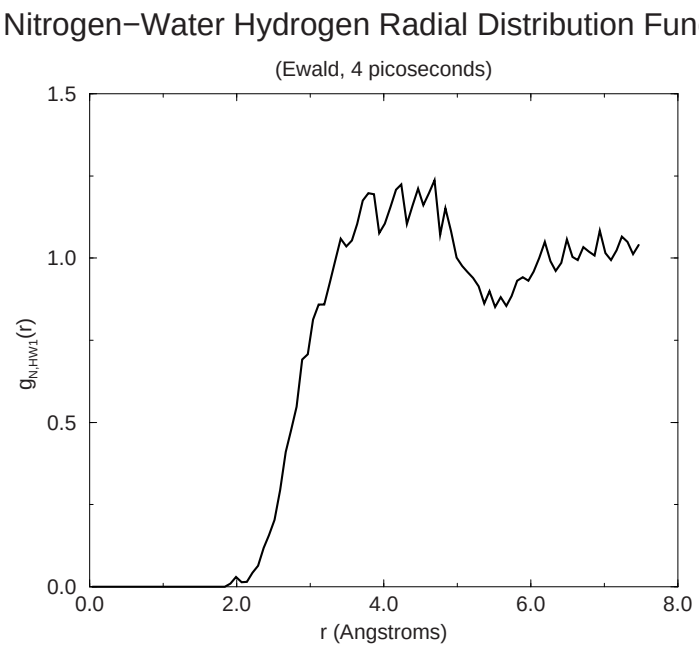
This step performs dynamic analysis of the solvent. The velocity autocorrelation function and its power spectrum are calculated and saved in tabular format. The processed plots are shown right after this listing.

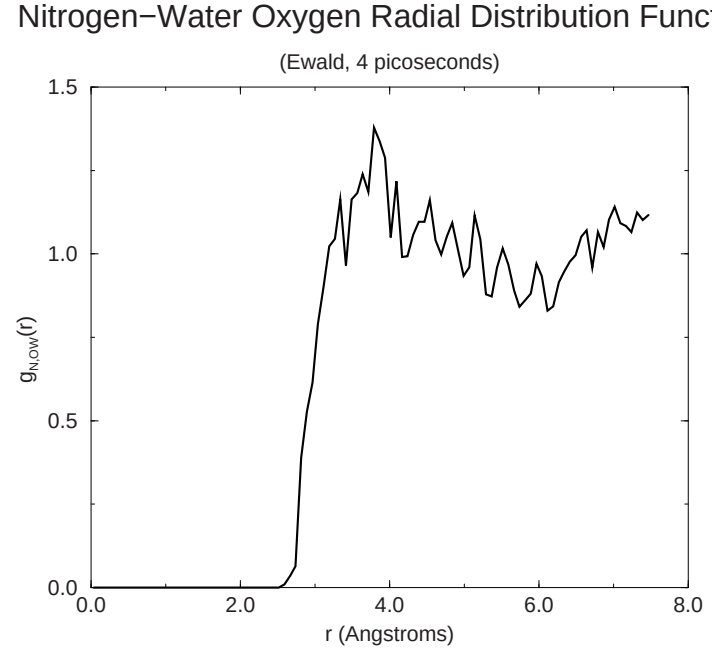
```
mdanalysis
  input trajectories nfiles 1 external fnames file glyh2o.trj -
    coordinates and velocities every 1 maxrec 2000 nskip 1 nobox delt 0.001 -
    rlow 0.0 rup 7.5 ngridr 100 -
    elow -100.0 eup 100.0 ngride 100 dw 1.0 msteps 2000
  dynamic solvation vcf plvcf wrvcf plspectrum wrspectrum -
     tabular file "vcf.gr" file "spec.gr"
  file close
quit
end
```

Here we show all the radial distribution functions, followed by the binding energy distribution functions, and then the velocity autocorrelation function. Plots like these can be generated by programs such as Gnuplot[3] and Grace[4]. The latter has a nice Motif-style graphical user interface.

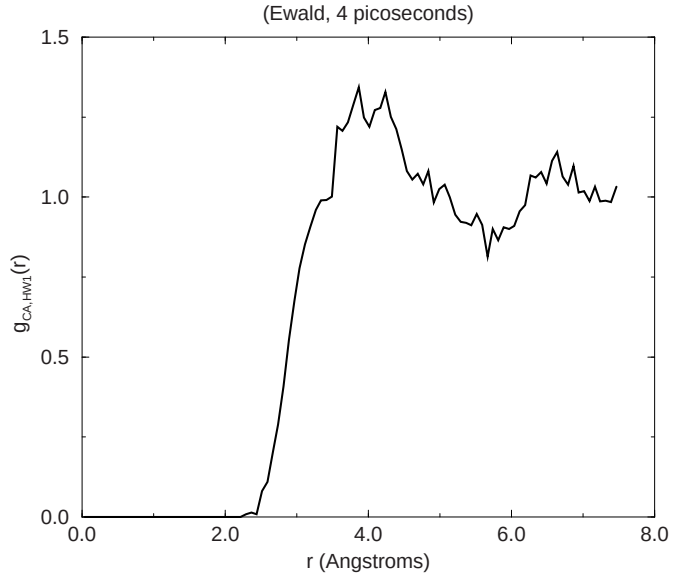
[3] http://www.gnuplot.info

[4] http://plasma-gate.weizmann.ac.il/Grace/

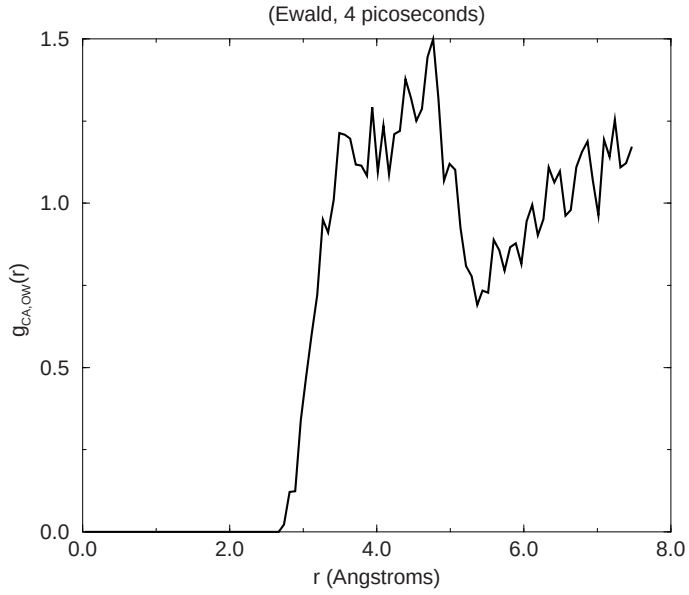

Nitrogen−Water Hydrogen Radial Distribution Function
(Ewald, 4 picoseconds)
1.5
1.0
0.5
0.0
$g_{N,HW1}(r)$
0.0
2.0
4.0
6.0
8.0
r (Angstroms)

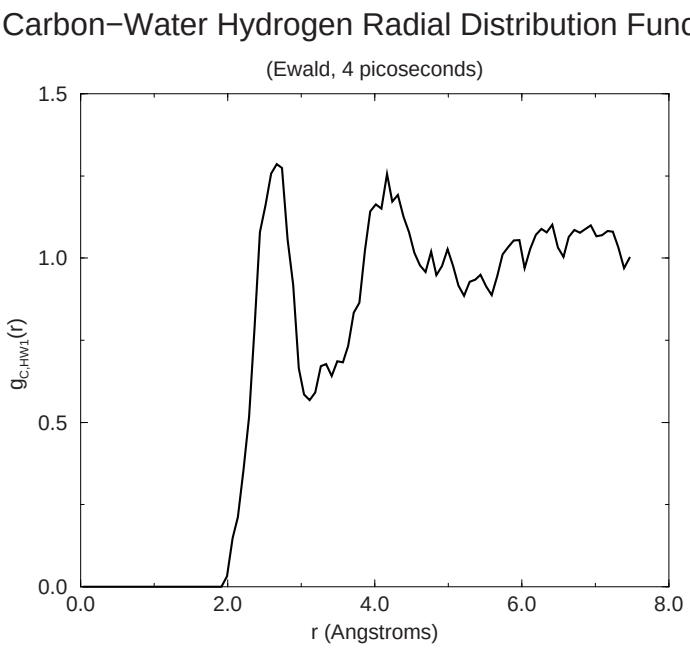

Nitrogen−Water Oxygen Radial Distribution Function
(Ewald, 4 picoseconds)
1.5
1.0
0.5
0.0
$g_{N,OW}(r)$
0.0
2.0
4.0
6.0
8.0
r (Angstroms)

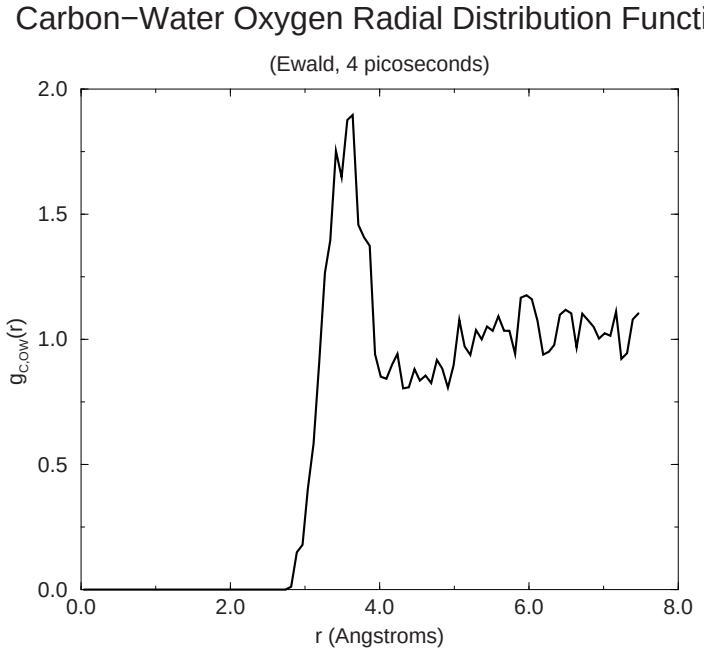
α Carbon−Water Hydrogen Radial Distribution Function

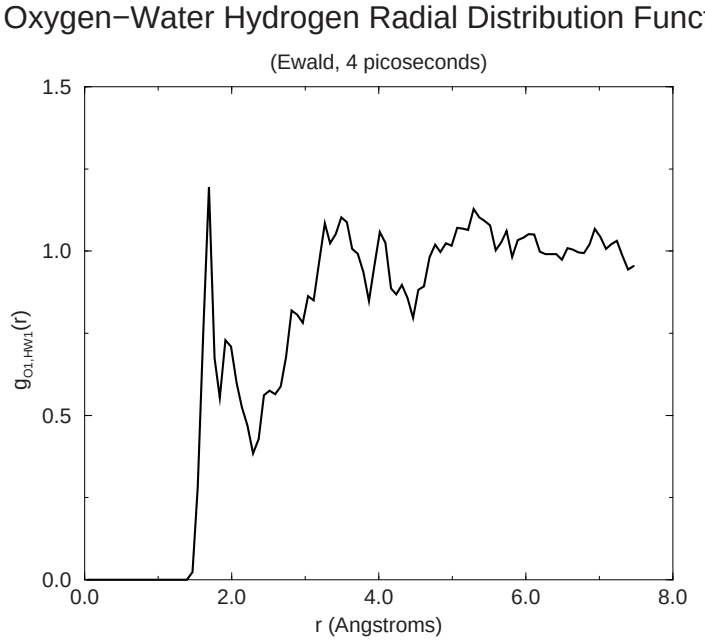


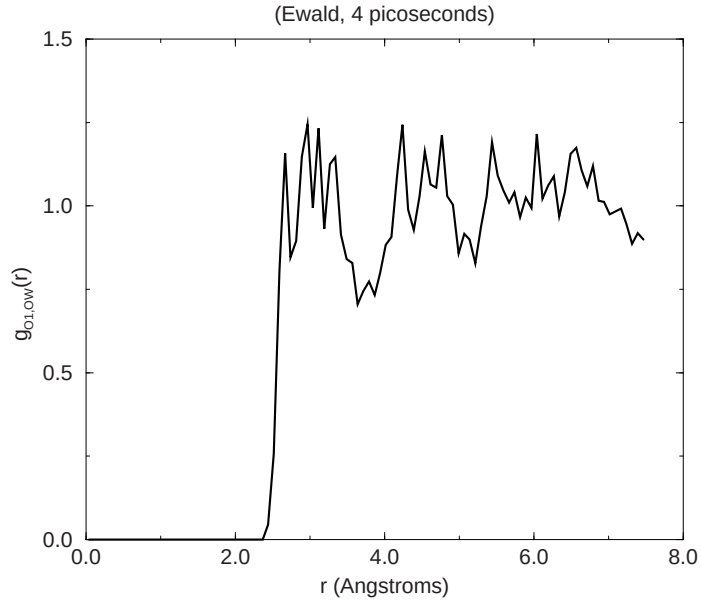
α Carbon−Water Oxygen Radial Distribution Function

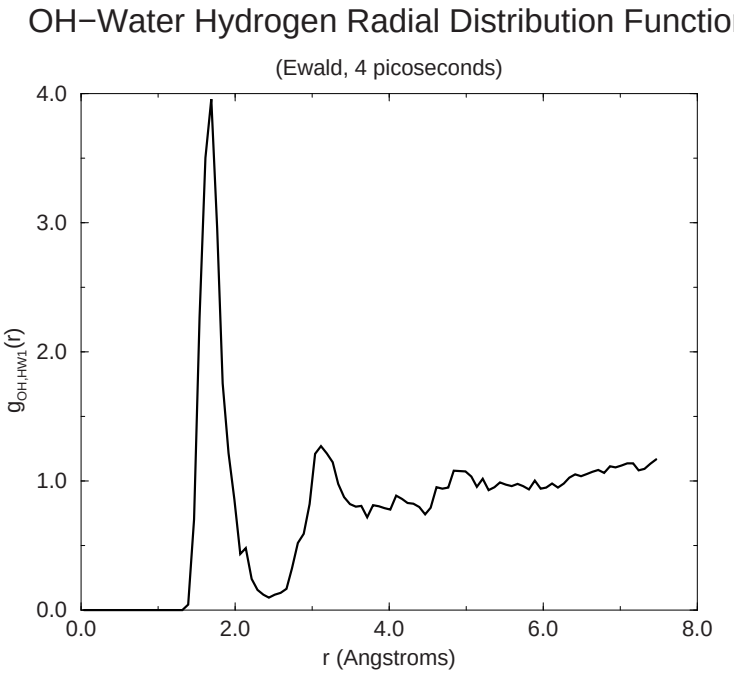


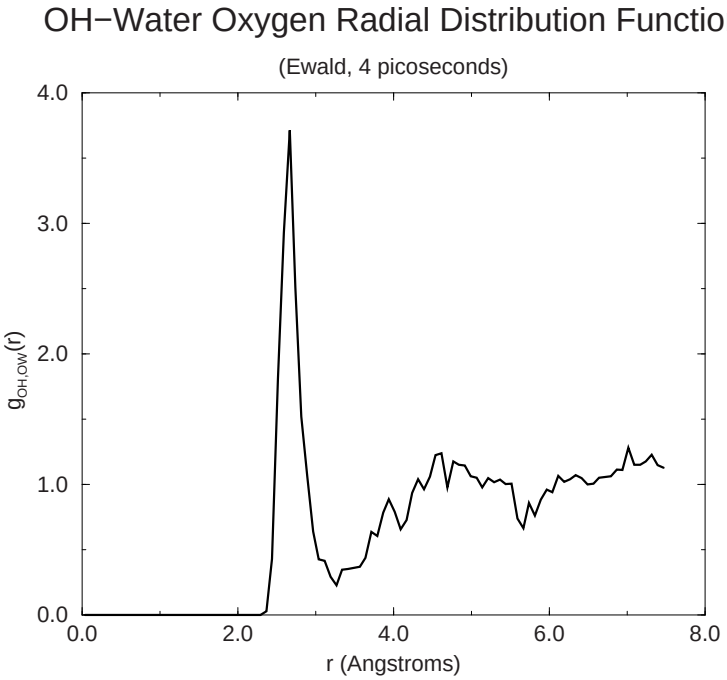

Carbon−Water Hydrogen Radial Distribution Function
(Ewald, 4 picoseconds)
1.5
1.0
0.5
0.0
$g_{C,HW1}(r)$
0.0
2.0
4.0
6.0
8.0
r (Angstroms)

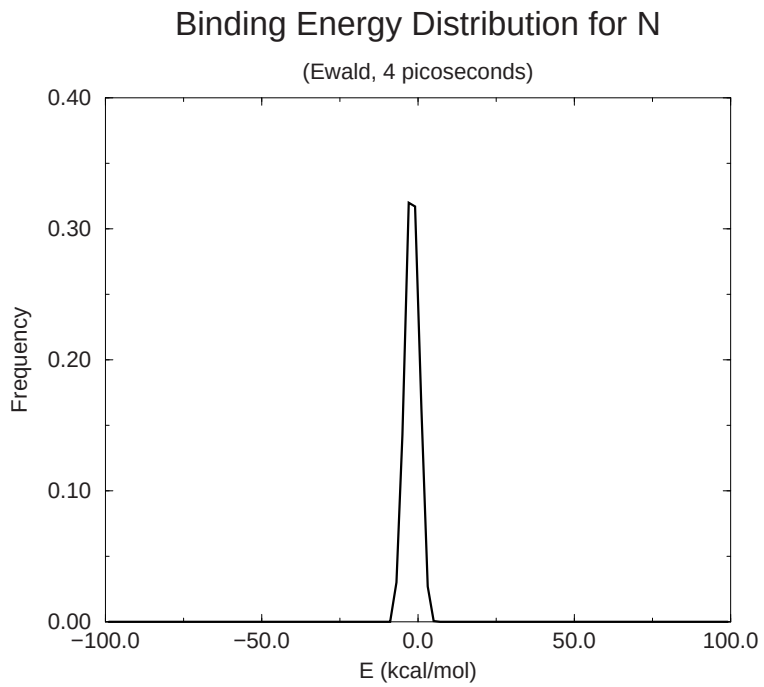

Carbon−Water Oxygen Radial Distribution Function
(Ewald, 4 picoseconds)
2.0
1.5
1.0
0.5
0.0
$g_{C,OW}(r)$
0.0
2.0
4.0
6.0
8.0
r (Angstroms)

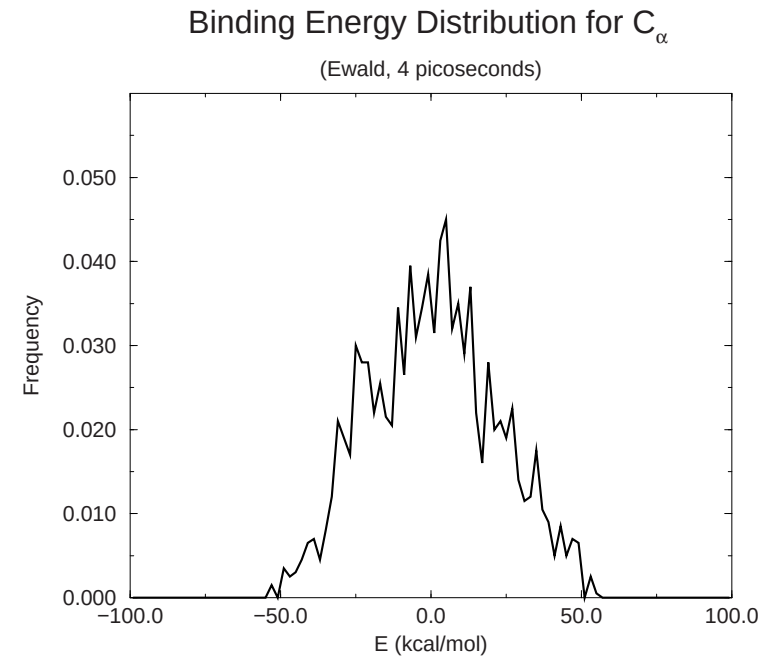

Oxygen−Water Hydrogen Radial Distribution Function
(Ewald, 4 picoseconds)
1.5
1.0
0.5
0.0
$g_{O1,HW1}(r)$
0.0
2.0
4.0
6.0
8.0
r (Angstroms)

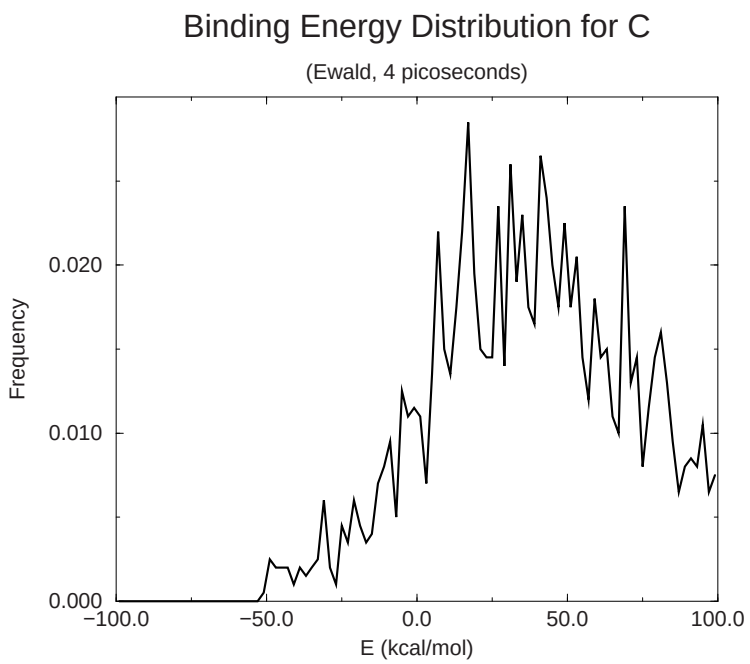

Oxygen−Water Oxygen Radial Distribution Function
(Ewald, 4 picoseconds)
1.5
1.0
0.5
0.0
$g_{O1,OW}(r)$
0.0
2.0
4.0
6.0
8.0
r (Angstroms)

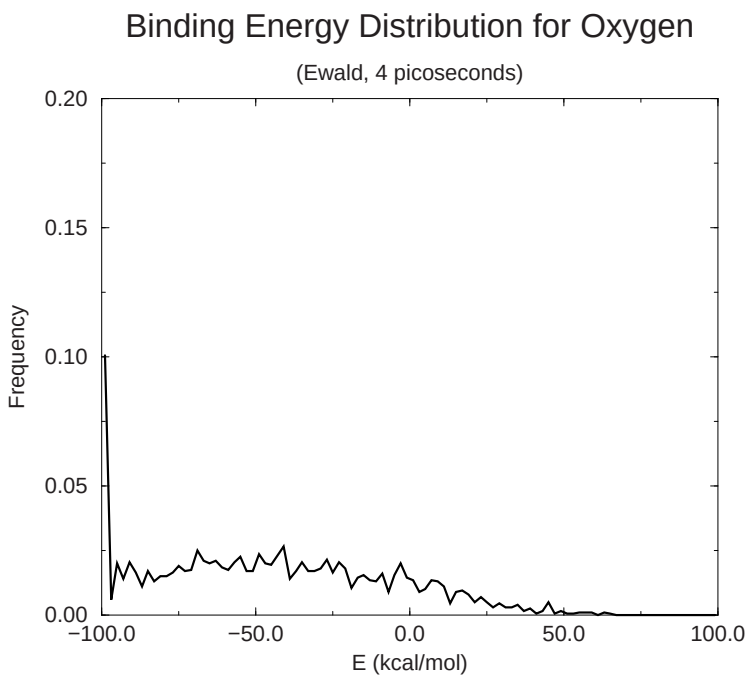

OH−Water Hydrogen Radial Distribution Function
(Ewald, 4 picoseconds)
4.0
3.0
2.0
1.0
0.0
g_OH,HW1(r)
0.0
2.0
4.0
6.0
8.0
r (Angstroms)

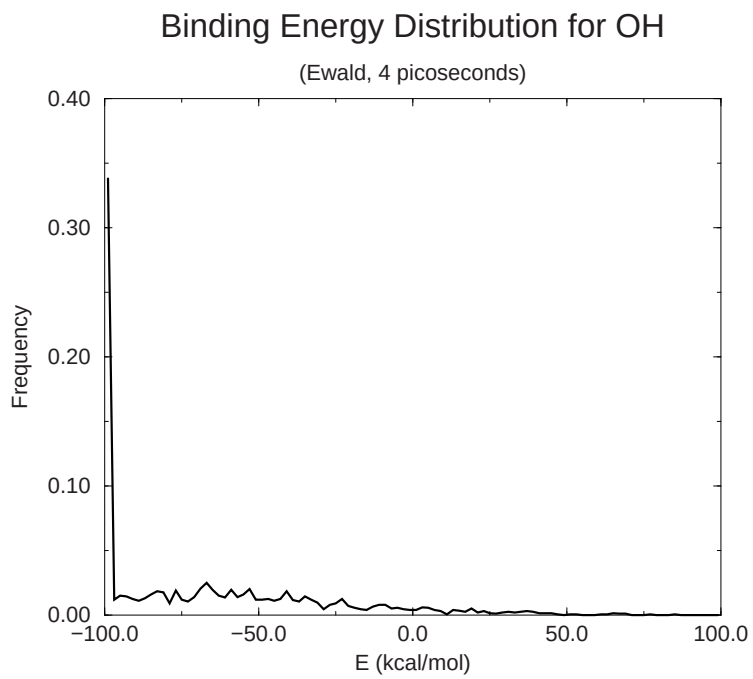

OH−Water Oxygen Radial Distribution Function
(Ewald, 4 picoseconds)
4.0
3.0
2.0
1.0
0.0
g_OH,OW(r)
0.0
2.0
4.0
6.0
8.0
r (Angstroms)

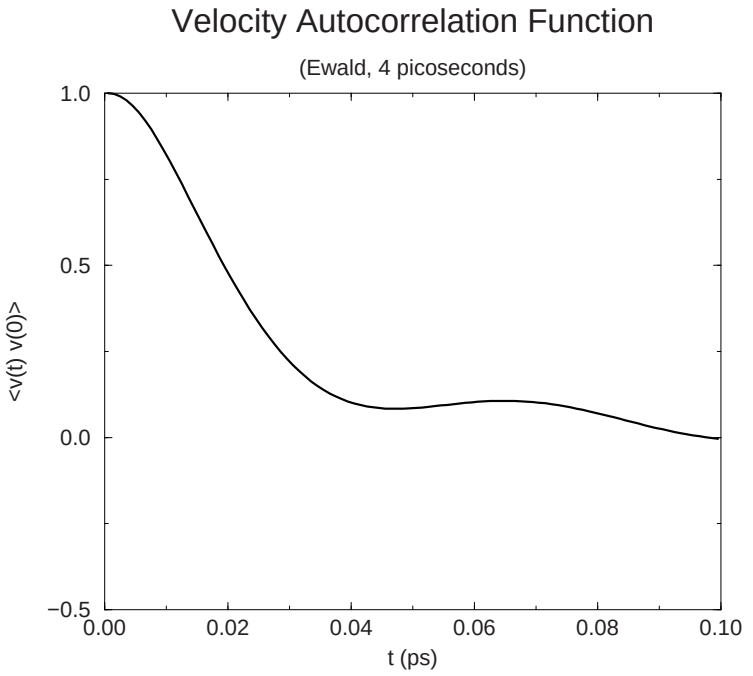

Binding Energy Distribution for N
(Ewald, 4 picoseconds)
Frequency
0.40
0.30
0.20
0.10
0.00
−100.0
−50.0
0.0
50.0
100.0
E (kcal/mol)

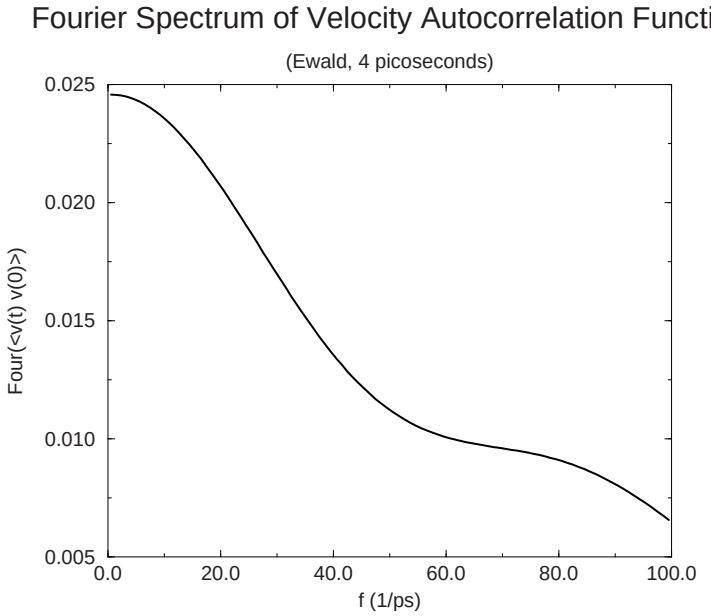

Binding Energy Distribution for Cα
(Ewald, 4 picoseconds)
Frequency
0.050
0.040
0.030
0.020
0.010
0.000
−100.0
−50.0
0.0
50.0
100.0
E (kcal/mol)


Binding Energy Distribution for C
(Ewald, 4 picoseconds)
Frequency
0.020
0.010
0.000
−100.0
−50.0
0.0
50.0
100.0
E (kcal/mol)


Binding Energy Distribution for Oxygen
(Ewald, 4 picoseconds)
Frequency
0.20
0.15
0.10
0.05
0.00
−100.0
−50.0
0.0
50.0
100.0
E (kcal/mol)


Binding Energy Distribution for OH
(Ewald, 4 picoseconds)
Frequency
0.40
0.30
0.20
0.10
0.00
−100.0
−50.0
0.0
50.0
100.0
E (kcal/mol)


Velocity Autocorrelation Function
(Ewald, 4 picoseconds)
<v(t) v(0)>
1.0
0.5
0.0
−0.5
0.00
0.02
0.04
0.06
0.08
0.10
t (ps)



C.3.5 Dipeptide/H2O MD Simulation and Analysis (NPT Ensemble)

This example illustrates the preparation of a protein/water system composed of the dipeptide ALA-GLY and a box of 196 SPC-type water molecules. Once the coordinate structures are built and molecular dynamics tasks have been performed, the `mdanalsysis` and `table` tasks, and `DICE` commands, are used to analyze the resulting trajectories. In this example, the system is prepared for a constant pressure molecular dynamics simulation.

Input files	
`rdfandrms.inp`	Main input file
`spchoh.dat`	Solvent coordinate file
`paramstd.dat`	Parameter file
`spcconst.dat`	Constraint file
`rdfandrms.rst`	Coordinate and velocity restart file
`mdagwat.inc`	MDAnalysis included file

Output files	
rdfandrms.out	Main output file
rdfandrms.trj	Coordinate and velocity trajectory file
int1c.dat	Integrated RDF data file
int1ca.dat	Integrated RDF data file
int1cb.dat	Integrated RDF data file
int1n.dat	Integrated RDF data file
int1o.dat	Integrated RDF data file
int2c.dat	Integrated RDF data file
int2ca.dat	Integrated RDF data file
int2n.dat	Integrated RDF data file
int2o.dat	Integrated RDF data file
rdf1c.dat	RDF plot file
rdf1ca.dat	RDF plot file
rdf1cb.dat	RDF plot file
rdf1n.dat	RDF plot file
rdf1o.dat	RDF plot file
rdf2c.dat	RDF plot file
rdf2ca.dat	RDF plot file
rdf2n.dat	RDF plot file
rdf2o.dat	RDF plot file

```
set FFIELD AMBER86
write file rdfandrms.out -
      title Dipeptide/H2O MD Simulation using DICE and MDANALYSIS *
```

Task `create` is used to build the initial dipeptide/water structure.

```
create
   build primary name dipep type protein ala  gly end
   build solvent name solvent1 type spc nmol 216 h2o
quit
```

Task `setmodel` initializes the energy function for this calculation. The coordinates of a 18.6206 Å cube of solvent in this example are read from the file, '`spchoh.dat`'. Periodic boundary conditions will be applied to nonbonded interactions between solvent molecules and nonbonded solute-solvent interactions. Nonbonded energy calculations between solvent molecules will use a molecular cutoff, and all nonbonded interactions will used a cutoff distance of 7.5 Å. `SHAKE` constraints for molecular dynamics are read from the file '`spcconst.dat`'.

```
setmodel
 setpotential
   mmechanics tail
 quit
 read parm file paramstd.dat noprint
```

```
 solvent old file spchoh.dat bx 18.6206 by 18.6206 bz 18.6206
 energy parm cutoff 7.5 listupdate 4 diel 1.0 nodistance print 100
 energy periodic name solvent1 bx 18.6206 by 18.6206 bz 18.6206
 energy molcutoff name solvent1
 energy constraint read file spcconst.dat
quit
minm
  conjugate dx0 0.1 dxm 1.0 rest 50
  input cntl mxcyc 1000 rmscut .05 deltae .001
  run
quit
```

The molecular dynamics simulation is performed starting from the coordinates and velocities in '`rdfandrms.dat`'. The trajectories for the simulation are saved in '`rdfandrms.trj`' every '`nskip`' iterations. The duration and the time step for the simulation are stored in '`time`' and '`delta`'. A 10 picosecond simulation is run, but using a time step of 4 femtoseconds. This time step is too large for the usual Verlet integrator (even when using `SHAKE`/`RATTLE`), so we use instead the r-RESPA integrator, but updating the bonding (`fast`) forces four times as often.

```
put 10 into 'nskip'
put 10.0 into 'time'
put 0.001 into 'delta'
put 'time' / 'delta' into 'nstep'
dynamics
  input cntl -
     nstep 'nstep' delt 'delta' relax 0.10 taup 0.10 -
     seed 100 stop rotations -
     constant temperature constant pressure -
     nprnt 50 tol 1.e-7 dvdp 4.96e-5 density 1.3 -
     initialize temperature at 50.0
  input cntl name solvent1 cmscale
  input cntl name dipep atscale
  input target temperature 298.0 pressure 1.0
!  read restart coordinates and velocities box -
!    formatted file rdfandrms.rst
  write trajectory coordinates box external -
    file rdfandrms.trj every 'nskip'
  run rrespa fast 4
  write restart coordinates and velocities box -
    formatted file rdfandrms.rst
quit
```

The radial distribution functions and the integrated radial distribution functions are calculated here for all of the heavy atoms on each residue. The `mdanalysis` parameters are contained in an the following included file:

```
:mdanallist
   input nfile 1 rlow 'rlow' rup 'rhigh' ngridr 50 maxrec 'maxrec' -
        nskip 'nskip' elow -50.0 eup 50.0 ngride 100 ngridt 100 -
        ngrida 100 delt 0.001 dw 1.0 -
        box coordinates every 50 -
        trajectory external fname file rdfandrms.trj
return
```

This following section of the input file uses a set of nested `DICE` `while` loops to create the lists of heavy atoms on each residue. These lists are passed to the `mdanalysis` task. Unique filenames for the rdf output plot files are created by `DICE` commands inside the inner while loop. At each step a couple of files containing, respectively, the rdf and its integral, are written out in `tabular` form.

```
put sizeof 'residues' into 'restot'
put 'nstep' / 'nskip' into 'maxrec'
put 2.0 into 'rlow'      ! parameters for rdf function
put 5.0 into 'rhigh'
put 1.0 into 'resn'      ! counter for residue number
put $rdf$ into 'start1'  ! initial string for output file names
put $int$ into 'start2'
while 'resn' le 'restot'
   put 'atoms' with species:1:residues:'resn':atoms:*: into 'temp'
   put 'temp' without atoms:h*: into 'temp'
   put sizeof 'temp' into 'tsize'
   if 'tsize' gt 0
      put 1 into 'i'
while 'i' le 'tsize'
         put index 'i' 'temp' into 'tempi'  ! get atom name character string
         put ( char 'resn' ) concat 'tempi' concat $.dat$  into 'endit'
         put 'start1' concat 'endit' into 'fname1'
         put 'start2' concat 'endit' into 'fname2'
         show 'fname1' 'fname2'
mdanalysis
            call mdanallist file mdagwat.inc
            static rdf iatom name dipep inres 'resn' atom 'tempi' end -
                   jatom name solvent1 jnres 1 atom ow end
            static rdf run -
            plrdf tabular file 'fname1' -
            file 'fname2'
            file close
```

```
quit
         put 'i' + 1 into 'i'
endwhile
endif
   put 'resn' + 1 into 'resn'
endwhile
```

Here, we calculate the RMS fluctuations with translations and rotations removed. Only species 1 is used in these calculations.

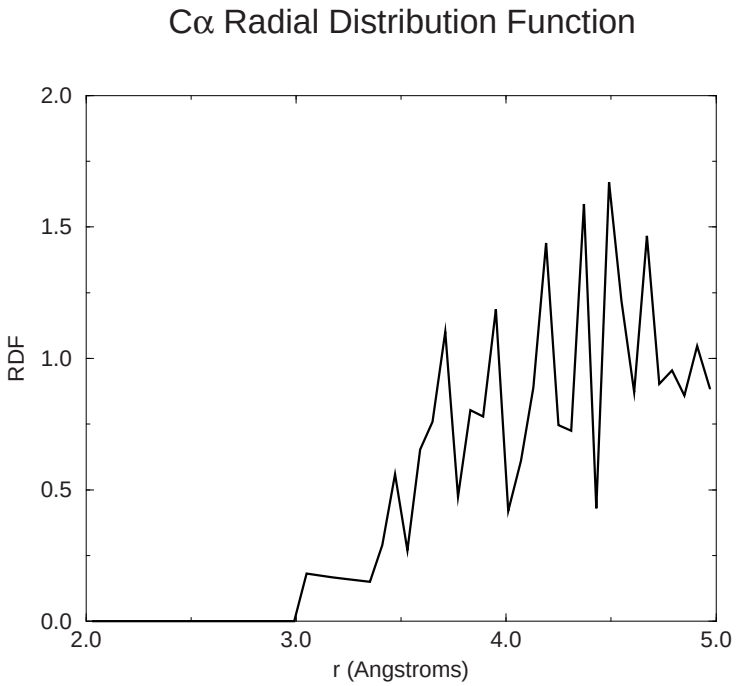
```
table
 traj nfile 1 maxrec 'maxrec' nskip 'nskip' delt 'delta' -
     coordinates every 'nskip' box trajectory -
     external fname file rdfandrms.trj
 put 0 into 'count'   ! first calculate avg structure
quit
put 0 into 'sumr'
put 0 into 'sumr2'
table
 starttrack
quit
   reset 'cord'
   put 'cord' with species:1: into 'tcord'
   put sum 'tcord' into 'top'
   put 'top' / ( sizeof 'tcord' ) into 'com'
   put 'tcord' - 'com' into 'tcord'
   put 'tcord' + 'sumr' into 'sumr'
   put 'count' + 1 into 'count'
table
 stoptrack
 close
quit
put 'sumr' / 'count' into 'avgr'
reset 'sumr'
```

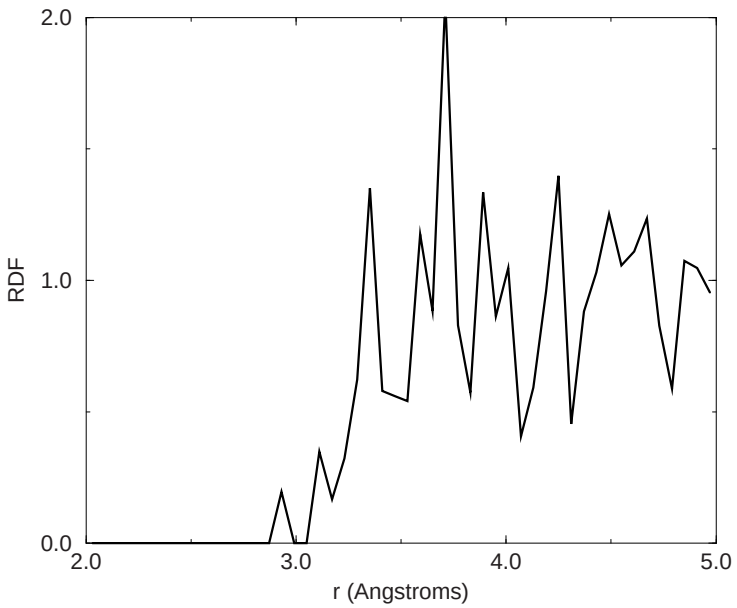
Now we find the best fit of each structure to the average structure and store the squares of the deviations from the average structure. The numbers given are in angstroms squared and represent the average squared deviation of the structure with rotational and translational motion removed.

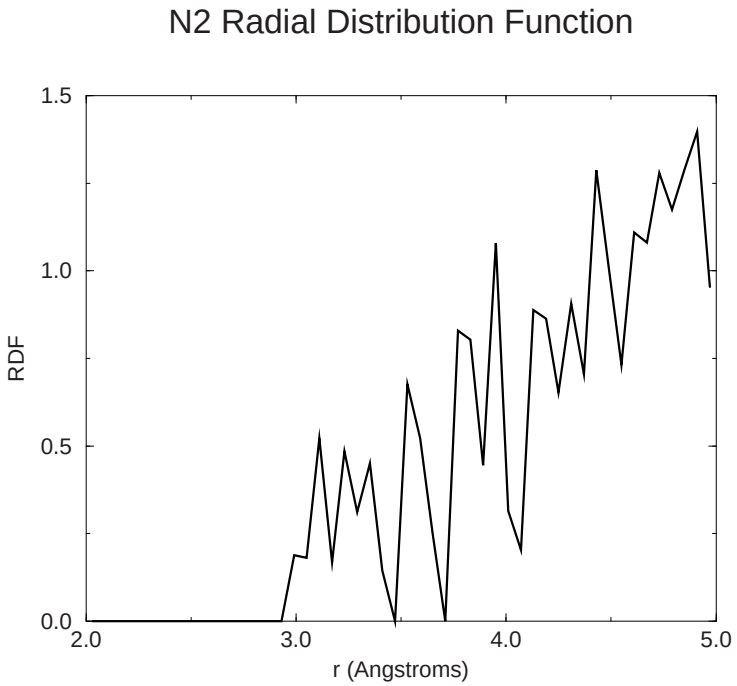
```
table
 traj nfile 1 maxrec 'maxrec' nskip 'nskip' delt 'delta' -
     coordinates every 'nskip' box trajectory -
     external fname file rdfandrms.trj
quit
put 0 into 'count'
put 0 into 'sumr'
```

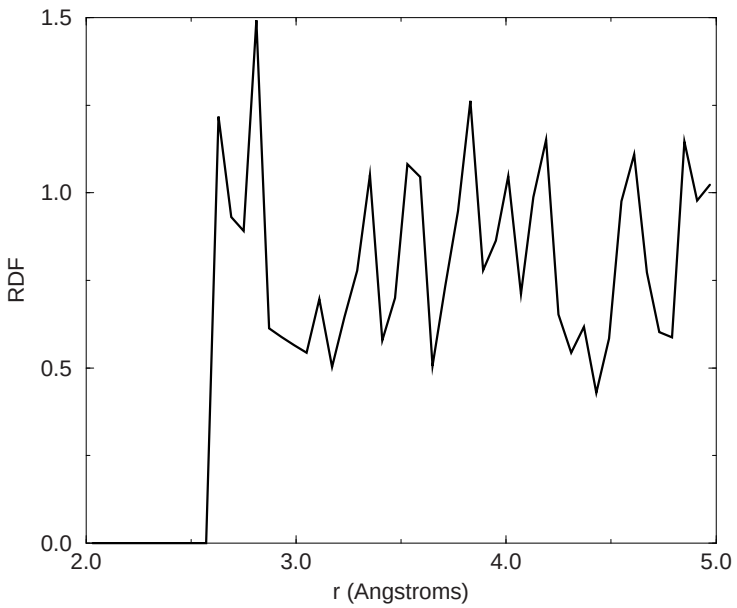
```
table
 starttrack
quit
   reset 'cord'
   reset 'newcord'
   reset 'r2'
   put 'cord' with species:1: into 'tcord'
   put rmsdev 'avgr' 'tcord' into 'newcord'
   put 'newcord' * 'newcord' into 'r2'
   put 'r2' + 'sumr2' into 'sumr2'
   put 'newcord' + 'sumr' into 'sumr'
   put 'count' + 1 into 'count'
table
 stoptrack
 close
quit
put 'sumr' / 'count' into 'avgr'                ! new average structure
put 'sumr2' / 'count' into 'sumr2'              ! average squared deviation for each atom
put 'sumr2' - 'avgr' * 'avgr' into 'msfluct'    ! calculate mean squared fluctuation
put 'msfluct_1' + 'msfluct_2' + 'msfluct_3' into 'msfluct'   ! sum components
put avg 'msfluct' by 'residues' into 'allres'   ! msfluct may be sorted by atoms,residues
                                                ! average by  residue
show 'allres'
end
```

The following plots were generated with an external 2D plotting program from the data printed out in tabular format above. Only some of the rdfs are shown for illustration.


Cα Radial Distribution Function
RDF
r (Angstroms)
0.0
0.5
1.0
1.5
2.0
2.0
3.0
4.0
5.0


Cβ Radial Distribution Function
RDF
r (Angstroms)
0.0
1.0
2.0
2.0
3.0
4.0
5.0


N2 Radial Distribution Function
RDF
r (Angstroms)
0.0
0.5
1.0
1.5
2.0
3.0
4.0
5.0


O2 Radial Distribution Function
RDF
r (Angstroms)
0.0
0.5
1.0
1.5
2.0
3.0
4.0
5.0

C.3.6 Surface Area Versus Solvation Energy for a Dipeptide

This example illustrates some of the features of the task `table` and task `analysis` in the calculation of the relationship between surface area and solvation energy for a dipeptide

Input files	
`alagly.inp`	Main input file
`spchoh.dat`	Solvent coordinate file
`paramstd.dat`	Parameter file
`spcconst.dat`	Constraint file
`alagly.rst`	Coordinate restart file

Output files	
`alagly.out`	Main output file
`hydr.gr`	Tabular data to be plotted

```
write file alagly.out -
      title Surface area versus solvation energy for a dipeptide *
```

Task `create` is used the build the initial dipeptide solvent system.

```
create
  build primary name solute1 type protein ala gly end
  build solvent name solvent1 type spc nmol 199 h2o
quit
```

The charges on each solute atom are copied to a new table named, '`cg`', and the charges of a single solvent molecule are copied to a new table named, '`cg1`'. These new tables are then printed.

```
table
  put 'charge' with species:solute1: into 'cg'
  put 'charge' with species:solvent1:molecules:1: into 'cg1'
  printoptions title Solute charges *
  print 'cg'
  printoptions title Solvent charges*
  print 'cg1'
quit
```

The energy function for the solute-solvent system is initialized.

```
setmodel
   setpotential
     mmechanics
```

```
    quit
    read parm file paramstd.dat noprint
    energy parm cutoff 7.5 listupdate 10 diel 1.0 nodistance
    energy periodic name solvent1 bx 18.6206 by 18.6206 bz 18.6206
    energy molcutoff name solvent1
    energy constraint read file spcconst.dat
quit
```

The system is minimized starting with the coordinates in the restart file '`alagly.rst`'.

```
minm
  input cntl mxcyc 50
  steep dx0 0.05 dxm 1.0
  read restart coordinates formatted file alagly.rst
  run
quit
```

The surface area and solvation energy for the solute are calculated for the minimized system.

```
analysis
  surface name solute1 echooff noprint
  energy solvation of name solute1 by name solvent1 scutoff 8.0
quit
```

The result of the surface area calculation after minimization, which is held in the internal table '`surfacearea`', is copied to a new table, '`sa1`', for all of the atoms of the solute species. The result of the solvation energy calculation, which is held in the the internal table '`hydration`', is copied to a new table, '`hydrone`', for all of the atoms of the solute species. These new tables are then printed and plotted in the output file.

```
table
  put 'surfacearea' with species:solute1: into 'sa1'
  put 'hydration'   with species:solute1: into 'hydrone'
  printoptions title Solvation energy of solute *
  print 'hydrone'
  printoptions title Surface area of solute *
  print 'sa1'
quit
```

Here, a short molecular dynamics simulation is run and then the surface areas and solvation energies are recomputed.

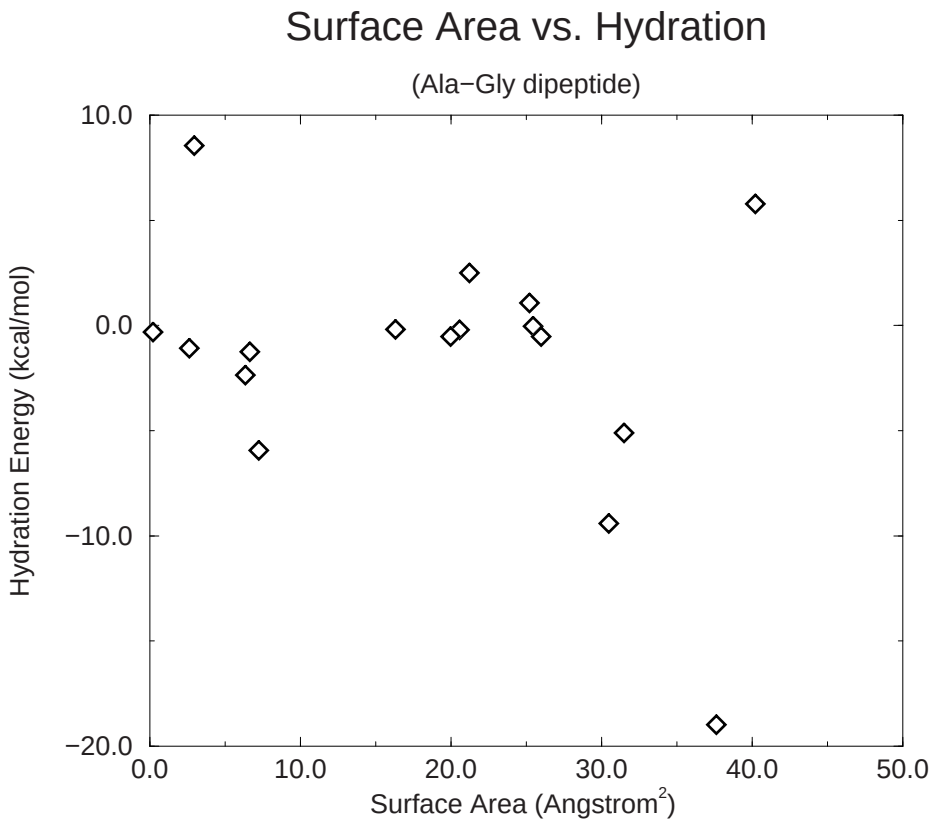
```
dynamics
  input cntl -
      nstep 50 delt 0.001 relax 0.01 -
      seed 100 constant temperature byspecies -
      initialize temperature at 298.0 -
```

```
        nprnt 5 tol 1.e-7
    input target temp 298.0 name solute1 temp 298.0 name solvent1
    run
quit
```

The result of the surface area calculation, which is held in the internal table '`surfacearea`', is copied to a new table, '`sa2`', for all of the atoms of the solute species. The result of the solvation energy calculation, which is held in the the internal table '`hydration`', is copied to a new table, '`hydrtwo`', for all of the atoms of the solute species. These new tables are printed in a tabular form in file '`hydr.gr`', which is then processed by Grace[5] to generate the PostScript plot that appears after this listing.

```
analysis
  surf name solute1 echooff noprint
  energy solvation of name solute1 by name solvent1 scutoff 8.0
quit
table
  put 'surfacearea' with species:solute1: into 'sa2'
  put 'hydration'   with species:solute1: into 'hydrtwo'
  printoptions title Solute solvation energy after dynamics *
  print 'hydrtwo'
  printoptions title Solute surface area after dynamics *
  print 'sa2'
  plot 'sa2' 'hydrtwo' tabular file hydr.gr
quit
end
```

[5] `http://plasma-gate.weizmann.ac.il/Grace/`



C.3.7 Dynamical Surface Area Calculation

In this example `DICE`, `table`, and `analysis` features are illustrated in the calculation of the surface area of an α-helical protein fragment during the course of a molecular dynamics simulation.

Input files	
`alphahelix.inp`	Main input file
`alphahelix.pdb`	Coordinate file (IMPACT format)
`paramstd.dat`	Parameter file
`alphahelix.rst`	Coordinate and velocity restart file

Output files	
`alphahelix.out`	Main output file
`alphahlx.meta`	Plot file (Meta format)
`ahelixrst1`	Coordinate and velocity restart files
`ahelixrst2`	Coordinate and velocity restart files
`ahelixrst3`	Coordinate and velocity restart files
`ahelixrst4`	Coordinate and velocity restart files
`ahelixrst5`	Coordinate and velocity restart files

```
write file alphahelix.out -
      title Dynamical Surface Area Calculation *
```

Task `create` is used to build the α helix protein fragment. In this example the sequence and the initial coordinates are read from the file, '`alphahelix.xyz`'.

```
create
 build primary name ahelix type protein read file alphahelix.xyz
 read coordinates name ahelix file alphahelix.xyz
quit
```

The energy function for this simulation is initialized using `setmodel`. `SHAKE` constraints are applied to both bonds and lone pairs.

```
setmodel
   setpotential
     mmechanics
   quit
   read parm file paramstd.dat noprint
   energy parm cutoff 7.5 listupdate 10 diel 1.0 distance
   energy constraint bond lonepair
quit
```

The table `'counter'` is a one dimensional integer table that is given an initial value of 1. This table is used as the control variable for the `while` loop.

```
put 1 into 'counter'
while 'counter' le 5
```

The table `'current'` is a one dimensional character table that holds a file name that identifies the restart file that will be written in this iteration. It is assigned the value of the character constant `'ahelixrst'` and the character representation of `'counter'`.

```
      put $ahelixrst$ concat char 'counter' into 'current'
```

Here, a short molecular dynamics simulation is run starting with the coordinates and velocities found on the restart file. The restart file is selected according to the value of `'counter'`.

```
dynamics
     input cntl -
       nstep 10 delt 0.001 relax 0.01 seed 100 stop rotations -
       constant temperature nprnt 20 tol 1.0e-7
     input target temperature 298.0 name ahelix
     if 'counter' eq 1
        read restart coordinates and velocities formatted file alphahelix.rst
     else
        read restart coordinates and velocities formatted file 'previous'
     endif
     run
     write restart coordinates and velocities formatted file 'current'
quit
```

Task `analysis` calculates the surface area with the current coordinates.

```
analysis
      surface name ahelix echooff noprint
quit
```

The surface area for the HN proton on methione(5) is copied into the table named `'temp'` and this table is appended to the table `'timesurf'`. The current value of the stored in `'counter'` is then appended to the table named `'time'`. The current file name is copied into the table named `'previous'` and the value of `'counter'` is incremented.

```
   put 'surfacearea' with residues:5:atoms:hn: into 'temp'
   put 'timesurf' append 'temp' into 'timesurf'
   put 'time' append 'counter' into 'time'
   reset 'surfacearea'
   put 'current' into 'previous'
   put 'counter' + 1  into 'counter'
endwhile
```

The contents of tables `'time'` and `'timesurf'` are printed in the output file, and the data from these tables is also written to the file '`alphahlx.meta`' in an `IMPACT` device independent format for subsequent plotting.

```
table
   plot 'time' 'timesurf' delay file alphahlx.meta
   print 'time' 'timesurf'
quit
end
```

C.3.8 Surface Area Statistics for Rhizopuspepsin

In this example, features of tasks `analysis` and `table` are illustrated in the calculation of the average surface areas for alanine and phenylalanine in the protein rhizopuspepsin.

Input files	
`rhizopus.inp`	Main input file
`2apr.pdb`	Coordinate file (PDB format)

Output files	
`rhizopus.out`	Main output file

```
write file rhizopus.out -
      title Statistics of Surface Areas for Rhizopuspepsin *
```

The structure of the protein is built using task `create`. In this example the sequence information and the coordinates are read from a Brookhaven PDB format file.

```
create
  build primary name rhizopus type protein read file 2apr.pdb
  read coordinates brookhaven name rhizopus file 2apr.pdb
quit
```

Calculate the surface area for this system and supress the detailed printing in this task.

```
analysis
  surface name rhizopus echooff noprint
quit
table
```

Calculate sum of the surface areas for each residue and store the result in the table named `'surfres'`.

```
  put sum 'surfacearea' by residues:*:  into 'surfres'
  print 'surfres'
```

Calculate surface area averages for all of the alanine and phenylalanine residues and store these results in the tables `'avgala'` and `'avgphe'`, respectively.

```
  put avg ( 'surfres' with residues:ala*: ) into 'avgala'
  put avg ( 'surfres' with residues:phe*: ) into 'avgphe'
```

Print the resulting tables of averages, `'avgala'` and `'avgphe'`.

```
  printoptions title Average surface area of alanine residues *
  show 'avgala'
  printoptions title Average surface area of phenylalinine residues *
  show 'avgphe'
quit
end
```

C.3.9 Normal Modes of Excited State Imidazole

In this example the normal modes and frequencies at the nuclear equilibrium positions in the first excited state of imidazole. The results of this calculation are retained for later use in a resonance raman calculation.

Input files	
`imdex.inp`	Main input file
`imdex.dat`	Residue topology file for excited state of imidazole
`imdexprm.dat`	Energy parameters for excited state of imidazole

Output files	
`imdex.out`	Main output file
`exmodes.dat`	Normal modes (frequencies and coordinates) for excited state
`imdex.rst`	Nuclear equilibrium configuration for excited state

It is a good idea to always tell `IMPACT` explicitly where to put the output, and to choose a descriptive title.

```
write file imdex.out -
      title Normal Modes of Excited State Imidazole*
```

Next, as usual, one has to `create` the molecule(s). In this case we are dealing with only one molecule (imidazole) and thus the creation is particularly simple.

```
create
  build newresidue imde file imdex.dat
  build primary type other name eximidazole imde end
quit
```

After the molecule has been created, and before doing anything involving energy (force) calculations, the energy model parameters have to be set. We choose the standard model (which has only harmonic bonds, angles and torsions) and read the parameters appropriate to the first electronic excited state from the file '`imdexprm.dat`', whose contents follow:

```
*
* Imidazole parameters
*
CC  12.01
CV  12.01
CR  12.01
H   1.008
HC  1.008
```

```
NA  14.01
NB  14.01
BOND
CR  -NB   475.       1.394        HIS(MOD)
CR  -NA   475.       1.411        HIS
CC  -NA   475.       1.387        HIS
CC  -CV   525.       1.452        HIS
CV  -NB   475.       1.363        ADE,GUA,HIS
CR  -HC   440.       1.080
H   -NA   334.       1.01         URA,GUA,HIS
CC  -HC   440.       1.080
CV  -HC   440.       1.080
THET
NA  -CR  -NB      70.        111.6    HIS(OL)
CC  -NA  -CR      70.        107.3       HIS(OL)
CV  -CC  -NA      70.        105.9     HIS(OL)
CC  -CV  -NB      70.        109.9     HIS(OL)
CR  -NB  -CV      70.        105.3      HIS(OL)
HC  -CR  -NB      30.        120.0
CR  -NA  -H       30.        126.35      HIS(OL)
HC  -CR  -NA      30.        120.0
CV  -CC  -HC      30.        119.7
HC  -CC  -NA      30.        120.0
CC  -CV  -HC      30.        120.0
HC  -CV  -NB      30.        120.0
CC  -NA  -H       30.        126.35      HIS(OL)
CC  -NA  -H       30.        126.35      HIS(OL)
CR  -NA  -H       30.        126.35      HIS(OL)
PHI
X   -CC  -CV  -X      4   14.3        180.          2.
X   -CC  -NA  -X      4    5.6        180.          2.
X   -CC  -NB  -X      2    4.8        180.          2.
X   -CR  -NA  -X      4    9.3        180.          2.
X   -CR  -NB  -X      2   10.0        180.          2.
X   -CV  -NB  -X      2    4.8        180.          2.
IPHI
X   -X   -NA  -H            1.0         180.         2.
X   -X   -NB  -H            1.0         180.         2.
X   -X   -C*  -HC           0.0         180.         2.
X   -X   -CR  -HC           1.0         180.         2.
X   -X   -CC  -HC           1.0         180.         2.
X   -X   -CV  -HC           1.0         180.         2.
NBON
```

```
C*   1.6481626  0.1200000   MISSING UNTIL 7/12/88 KOLLMAN(85)
CC   1.6481626  0.1200000   MISSING UNTIL 7/12/88 KOLLMAN(85)
CR   1.6481626  0.1200000   MISSING UNTIL 7/12/88 KOLLMAN(85)
CV   1.6481626  0.1200000   MISSING UNTIL 7/12/88 KOLLMAN(85)
H    0.8908987  0.0200000
HC   1.3719840  0.0100000   CHANGED FROM(1.225,0.1520) TO KOLLMAN(85)
N*   1.5590728  0.1600000   MISSING UNTIL 7/12/88 KOLLMAN(85)
NA   1.5590728  0.1600000   MISSING UNTIL 7/12/88 KOLLMAN(85)
NB   1.5590728  0.1600000
HBON
H   -NB     7557.00   2385.00
END
setmodel
  setpotential
    mmechanics
  quit
  read parm file imdexprm.dat noprint
  energy parm cutoff 7.5 listupdate 5 diel 1.0 nodistance print 200
quit
```

Since we are going to compute the normal modes and equilibrium configuration it is essential that we first minimize the energy. If this is not done the resulting normal modes will not be correct. After the minimization is done we write the equilibrium nuclear configuration to the file '`imdex.rst`', which will be read in during the resonance raman calculation.

```
minm
  conjugate dx0 0.005
  input cntl mxcyc 1500 rmscut 0.000001 deltae 0.000001
  write restart coordinates formatted file imdex.rst
  run
quit
```

After the minimization we can call `rraman` to compute the normal modes (and frequencies) and write them out to '`exmodes.dat`'.

```
rraman
  exc file exmodes.dat
end
```

C.3.10 Normal Modes for Methylamine

This example describes how to perform a normal mode calculation on an isolated molecule. The molecule chosen is methylamine, whose 7 atoms make it small enough for a simple example and large enough to make it nontrivial to obtain the normal modes (although symmetry considerations might help a lot in an analytic calculation). The normal mode calculation

is performed with the task `nmodes` after the molecule has been built (with `create`) and its energy parameters set (with `setmodel`). Once the normal modes have been determined one can request that the contribution of each internal degree of freedom (bonds, angles, etc.) to each and every mode be displayed (or written to the log file) with the subtask `ped`. This is a very useful option since it allows for a quick determination of the localized vibrational modes, easier to deal with than a list of (cartesian) displacements (which is, however, also generated).

Input files	
`normodes.inp`	Main input file
`mta.dat`	Residue topology file for methylamine
`mta.pdb`	Coordinates file (PDB format)
`mtaparam.dat`	Energy parameter file

Output files	
`normodes.out`	Main output file

Always tell `IMPACT` where to put the log information.

```
write file normodes.out -
      title Normal Modes for Methylamine *
```

Before performing any computation one has to build (`create`) the molecule.

```
create
  build newresidue mta file mta.dat
  build primary type other name mamine mta end
  read coordinates name mamine file mta.pdb
quit
```

Most of the time the energy model used is standard.

```
setmodel
  setpotential
   mmechanics
  quit
 read parm file mtaparam.dat noprint
 energy parm cutoff 7.5 listupdate 5 diel 1.0 nodistance scr14 1.0
quit
```

Every time normal modes are calculated it is essential to perform a potential energy minimization beforehand to make sure that the configuration used corresponds to equilibrium.

```
minimize
 conjugate dx0 0.005
```

```
input cntl mxcyc 2000 rmscut 0.000001 deltae 0.000001
run
quit
```

Now we compute the normal modes and their frequencies. The list of modes will appear in the main output file, '`nmodes.out`'. The subtask `ped` requests that a list of the percentage of potential energy in each internal degree of freedom for each mode be written also (this is called a Potential Energy Distribution).

```
nmodes
  ped
end
```

C.4 New Techniques

C.4.1 MD Simulation with the FMM

This example illustrates how to run a simulation using the Fast Multipole Method (FMM) in combination with the reversible Reference System Propagator Algorithm (r-RESPA). A simple (and small) system of about 216 water molecules is used, and a one picosecond simulation is run. Although the FMM is not very efficient for such a small system, in combination with the r-RESPA integrator it yields an algorithm that is about as fast as the usual Verlet plus cutoff method.

Input files	
`fmm.inp`	Main input file
`paramstd`	Energy parameter file
`tip4p.con`	Energy constraints
`tip4p.eq`	Coordinate and velocity restart file

Output files	
`fmm.out`	Main output file

```
write file fmm.out -
   title TIP4P Water MD *
```

As in the previous example, we first create a system of 216 `TIP4P` water molecules.

```
create
   build solvent name solvent1 type tip4p nmol 216 h2o
quit
setmodel
   setpotential
```

This is how the Fast Multipole Method (FMM) is selected. The parameter following the keyword `level` is the depth of the tree minus 1, and should always be larger or equal to 2. The depth of the tree should be chosen with two requirements in mind: (a) there is a speed and accuracy tradeoff between the depth of the tree and the number of multipoles that are needed; and (b) as a rule of thumb, since the Lennard-Jones interactions are computed together with the direct electrostatic contributions, twice the smallest box (that is, the size of a cluster at the deepest level) should be a little larger than the Lennard-Jones cutoff. The parameter following the keyword `maxpole` gives the order of the multipolar expansion that will be used, and

it must be larger or equal to 4 (one beyond hexadecupole). The keyword `smoothing` should be used if one is interested in a stable, energy-conserving simulation and the r-RESPA integrator with a time step of more than about 3 femtoseconds is used.

```
    mmechanics fmm level 2 maxpole 7 smoothing
  quit
  read parm file paramstd noprint
   enrg parm cutoff 9.5 listupdate 1 diel 1.0 nodist
   enrg periodic name solvent1 bx 18.6353 by 18.6353 bz 18.6353
```

`TIP4P` must be constrained, so we read the constraint file '`tip4p.con`'. Note also that a molecular cutoff is selected for the solvent; however, when using the FMM this is completely ignored.

```
   enrg cons read file tip4p.con
   enrg molcut name solvent1
quit
dynamics
```

We use this example also as a test of energy conservation, so let's run a one picosecond simulation at constant energy. Note that we use a large time step: ten femtoseconds!

```
input cntl -
    nstep 100 delt 0.01 relax 0.05 taup 0.10 seed 100 stop rotations -
    constant totalenergy nprnt 10 tol 1.e-7
read restart coordinates and velocities box real8 -
  external file tip4p.eq
```

We can use such a large time step because the FMM works nicely in concert with the reversible RESPA integrator. Here we run the simulation updating the bonding interactions every 10/16 femtoseconds, and the short-range nonbonded interactions (electrostatic and van der Waals) every 10/4 femtoseconds. The medium- and long-range are updated every step, that is, every 10 femtoseconds. Surprisingly, perhaps, this run shows a decent level of energy conservation. Increasing the `maxpole` would give, of course, a much more stable simulation, but it would also increase the runtime.

```
  run rrespa fast 4 medium 4
quit
end
```

C.4.2 Minimization using Implict Solvent (SGB)

Conjugate gradient minimization using the Surface Generalized Born Model (Sgb) is demonstrated here for the protein crambin.

Input files	
`sgb.inp`	Main input file
`paramstd`	Energy parameter file
`sgb.param`	Sgb parameter file
`sgb.prr.str.prm.real`	Sgb file
`sgb.slr_param`	Sgb file
`sgb.sncorrfnprm`	Sgb file
`sgb.sncorrfnprm.noself`	Sgb file
`sgb.sncorrfnprm.self`	Sgb file
`1crn.pdb`	Crambin Pdb file

Output files	
`sgb.out`	Main output file

The first executable block of the input file reads the Crambin pdb file to establish the system to be minimized.

```
CREATE
  build primary name crn type protein -
        read file 1crn.pdb crosslink
  read coordinates name crn file 1crn.pdb
  build crosslink automatic
  build types name crn
QUIT
```

The second executable block sets up the OPLS force field, informs the program to use a continuum solvent model, and initializes several parameters used in the calculation of the long-range interactions.

The 'consolv sgb' line instructs the program to use the continuum model based on the Surface Generalized Born Model equations (as opposed to the Poisson-Boltzmann continuum model).

```
SETMODEL
  setpotential
  mmechanic consolv sgb
  quit
  read parm file paramstd.dat noprint
  energy parm cutoff 12.5 -
         listupdate 20 diel 1.0 nodist
QUIT
```

The last block performs the actual minimization and writes out the final coordinate file.

```
MINM
  conjugate dx0 0.1 dxm 1.0 rest 50
```

```
  input cntl mxcyc 3000 rmscut .05 deltae .001
  run
  write pdb coordinates file crn_sgb_minimized.pdb name crn
QUIT
```

C.4.3 Minimization using Implict Solvent (PBF)

Conjugate gradient minimization using the Poisson-Boltzmann solver (PBF) is demonstrated here for the protein crambin.

Input files	
`pbf.inp`	Main input file
`paramstd`	Energy parameter file
`pbf.com`	Pbf command file
`pbf.prm`	Pbf parameter file
`1crn.pdb`	Crambin Pdb file

Output files	
`pbf.out`	Main output file

The first executable block of the input file reads the Crambin PDB file to establish the system to be minimized.

```
CREATE
  build primary name crn type protein -
        read file 1crn.pdb crosslink
  read coordinates name crn file 1crn.pdb
  build crosslink automatic
  build types name crn
QUIT
```

The second executable block sets up the OPLS force field, informs the program to use a continuum solvent model, and initializes several parameters used in the calculation of the long-range interactions.

The `consolv pbf` line instructs the program to use the continuum model based on the Poisson-Boltzmann equations (as opposed to the surface generalized Born continuum model). In a typical minimization, the calculation of the reaction-field energy and gradients by PBF are by far the most expensive part of the minimization. To reduce the required computational effort, the user may provide a cutoff parameter which specifies the maximum distance any solute atom must move relative to those used in the previous PBF calculation before a new PBF energy and gradient are calculated. If all atoms

have moved less than this cutoff value relative to the previous pbf calculation, then the previously calculated pbf energy and forces are used without calling the pbf module. This protocol is based on the observation that the reaction-field energy and gradient are both slowly-varying functions of the atomic coordinates for proteins, and hence do not need to be updated every minimization step to achieve reasonably accurate results. In the input file fragment below, the cutoff is set to 0.2 Å; the default is 0.1 Å. A larger cutoff value would, of course, reduce the required CPU time even further, but with a loss in accuracy.

The other parameter on the `consolv` line is the `debug` flag. If the `debug` value is nonzero, then PBF will print out debugging information. The default value for the `debug` flag is 0 (off).

A dielectric constant of 2.0 (`diel 2.0`) is used here. The dielectric constant value is used for both the atom-atom electrostatic interactions and the electrostatic interactions between the atoms and the induced surface charges calculated by pbf (the reaction-field interactions). The dielectric value set here overrides the one specified in the file '`pbf.com`' in the '`$SCHRODINGER/impact-v3.0/opls/data`' directory. The default value is 1.0.

The only other major parameters in the files
'`$SCHRODINGER/impact-v3.0/opls/pbf.com`' and
'`$SCHRODINGER/impact-v3.0/opls/pbf.prm`' which a user might want to modify are the solvent radius and dielectric constant (both in '`pbf.com`' on lines 11 and 13). The current radius is set to 1.4 Å, and the solvent dielectric constant is set to 80.0, both are values typically used for water.

```
SETMODEL
  setpotential
  mmechanic consolv pbf cutoff 0.2 debug 0
  quit
  read parm file paramstd.dat noprint
  energy parm cutoff 12.5 -
         listupdate 20 diel 2.0 nodist
QUIT
```

The last block performs the actual minimization and writes out the final coordinate file. One important point to make here is that the `rmscut` value (the cutoff value for the RMS value of the gradient which is used in determining when to stop the minimization) is somewhat larger than what is often used. This is due to the fact that the gradient calculated by pbf can be 'noisy'. Hence using a small value for the acceptable RMS gradient may cause the program to 'bounce around' the minimum in an effort to achieve a unattainable goal, thereby wasting CPU time.

```
MINM
  conjugate dx0 0.1 dxm 1.0 rest 50
```

```
  input cntl mxcyc 3000 rmscut .10 deltae .001
  run
  write pdb coordinates file crn_minimized.pdb name crn
QUIT
```

C.4.4 S-Walking method with HMC

This example illustrates how to run a simulation using the Hybrid Monte Carlo with S-Walking method. A small pentpeptide (Met-Enkaphalin) is used for illustration.

Input files	
`swalk.inp`	Main input file
`paramstd`	Energy parameter file
`pentpep.rst`	Coordinate and velocity restart file

Output files	
`swalk.out`	Main output file

```
write file swalk.out -
   title HMC with S-Walking *
create
   build primary name pentpep type protein read file pentpep.pdb
   read coordinates name pentpep brookhaven file pentpep.pdb
   build types name pentpep
quit
setmodel
   setpotential
      mmechanics
   quit
   read parm file paramstd.dat noprint
   solute translate rotate diagonal
   enrg parm cutoff 25.0 -
     listupdate 100000 diel 1.0 nodist print 200
quit
minimize
   input cntl mxcyc 200
   steepest dx0 0.05 dxm 1.0
   run
quit
```

S-Walking method runs two walkers in tandem, and calls a local minimizer (steepest decent or conjugate gradient) every once a while to minimize the high-temperature J-walker's configuration to a local minimum. These commands specify the minimization method and the number of minimization steps. This is the same as a regular minimization process.

```
dynamics
   input cntl nstep 100000 delt 0.0015 relax 0.01 seed 101 -
     constant hmc nmdmc 5 swalk 1 minimize 1 stepgap 50000 steprec 100 -
   tempj 1000.0 nprnt 100 metric 0 tol 2.0e-7
```

The command 'const hmc' selects the HMC method rather than normal MD methods. HMC is similar to a constant temperature, constant volume (canonical ensemble) MD simulation. Keyword 'swalk' and 'minimize 1' selects S-Walking method. Consult description in 'Task Molecular Dynamics' for values of 'stepgap' and 'steprec'.

```
   input target temperature 300.0
   read  restart coordinates and velocities formatted file pentpep.rst
   run
   write pdb brookhaven name pentpep file pentpep.pdb
quit
end
```

C.4.5 Liaison: Linear Response Method Simulations

This example illustrates how to perform a single Liaison Linear Response Method (LRM) simulation for binding free energies. The method is also called Linear Interaction Approximation (LIA). Normally a set of these calculations is performed on different ligands, and their results are used to fit parameters which are then applied on other ligands to predict their binding energies.

The easiest way to set up Liaison simulations, fitting calculations, and binding energy predictions is through the Maestro graphical user interface; please see the *FirstDiscovery Quick Start Guide* and the *FirstDiscovery User Manual* for more up-to-date information about Liaison calculations. The directory '`samples/liaison/`' in the FirstDiscovery installation includes a full set of input and output files for a series of HEPT analogs binding to HIV-RT. The directory illustrates how the files are arranged so that the *simulate*, *fit*, and *predict* parts of a full Liaison simulation can interoperate. The *FirstDiscovery Technical Notes* discusses the entire workflow; the material below only documents the free and bound state simulations for the H01 ligand.

Two separate simulations per ligand must be run to estimate the binding energy: ligand in pure solvent (free state), ligand in protein and solvent complex (bound state). The binding energy can be estimated by:

$$\Delta G = \alpha(\langle U^b_{vdW}\rangle - \langle U^f_{vdW}\rangle) + \beta(\langle U^b_{elec}\rangle - \langle U^f_{elec}\rangle) + \gamma(\langle U^b_{cav}\rangle - \langle U^f_{cav}\rangle)$$

Input files	
`H01.bound.inp`	Bound state input file
`H01.free.inp`	Free state input file
`H01_lig.mae`	Ligand coordinate file
`H01_rec.mae`	Receptor coordinate file

Output files	
`H01.bound.out`	Bound state output file
`H01.bound.log`	Bound state log file
`H01.bound.ave`	Bound state averages
`H01.free.out`	Free state output file
`H01.free.log`	Free state log file
`H01.free.ave`	Free state averages
`H01_rec_min.mae`	Receptor minimized structure
`H01_lig_min.mae`	Ligand minimized structure

This input file '`H01.bound.inp`' is for the ligand in the *bound* state, i.e., ligand bound in the protein receptor in solvent. It uses a simple minimization protocol; dynamics and HMC simulations are also available.

```
write file "H01.bound.out" title Binding Energy *
create
  build primary name prot type auto read maestro file "H01_rec.mae"
  build types name prot
  build primary name drug type auto read maestro file "H01_lig.mae"
  build types name drug
quit
setmodel
   setpotential
     mmechanics consolv sgb
   quit
   read parm file paramstd.dat noprint
   enrg parm residue cutoff 15 -
     listupdate 10 diel 1 nodist print 10
   zonecons auto
quit
minimize
 input cntl mxcyc 5000 rmscut 0.05 deltae 1.0e-5
 conjugate dx0 0.05 dxm 1.0
```

```
 run
 write name prot maestro file "H01_rec_min.mae"
 write name drug maestro file "H01_lig_min.mae"
quit
```

Run LRM (LIA) simulation. The user should specify the ligand in the LRM simulation in order to collect interactions between ligand and its environment. The LRM ligand can be anything in the program's point of view, or example, it can be one ligand, or two ligands, or even a protein.

```
LRM
 assign ligand name drug
 input cntl average every 1 file "H01.bound.ave"
```

Choose a sampling method. This example selects Hybrid Monte Carlo (`hmc`) for underlying sampling engine. The other supported sampling methods are Molecular Dynamics and Monte Carlo.

```
!! Carry out 10 hmc sampling steps at 10 deg C
!! to get needed quantities needed for LIA fitting
 sample hmc
 input cntl mxcyc 5 nmdmc 2 delt 0.0005 -
 relax 0.01 nprnt 100 seed 101
 input target temperature 10.0
 run rrespa fast 2
QUIT


END
```

The following is the input file '`H01.free.inp`' for the ligand in the *free* state. It is very similar to the above input file for the bound state, except that it has no protein specific input commands.

```
write file "H01.free.out" title Binding Energy *


create
 build primary name drug type auto read maestro file "H01_lig.mae"
 build types name drug
quit
setmodel
   setpotential
     mmechanics consolv sgb
   quit
   read parm file paramstd.dat noprint
  enrg parm residue cutoff 15 listupdate 10 diel 1 nodist print 10
quit
minimize
 input cntl mxcyc 5000 rmscut 1.000000e-02 deltae 1.000000e-05
```

```
  conjugate dx0 5.000000e-02 dxm 1.000000e+00
 run
quit

lrm
 assign ligand name drug
 input cntl average every 10 file "H01.free.ave"
 sample hmc
 input cntl mxcyc 10 nmdmc 5 delt 0.0005 -
   relax 0.01 nprnt 100 seed 101 -
   constant temperature
 input target temperature 10.0
 run rrespa fast 2
quit
end
```

C.4.6 QSite: QM-MM Simulations

This section illustrates how to use QSite to do a QM-MM dynamics and geometry optimizations. See the QSite section in `SETMODEL` task for QSite related commands.

The easiest way to set up QSite simulations is through the Maestro graphical interface; please see the *FirstDiscovery Quick Start Guide* and the *FirstDiscovery Technical Notes* for more up-to-date information about QSite simulations than is described here.

Input files	
`qmmm-impact.inp`	Impact input file
`qmmm-jaguar.in`	Jaguar input file
`leu.mae`	Input structure

Output files	
`qmmm.out`	Impact output file
`qmmm-jaguar.out`	Jaguar output file
`leu_out.mae`	Final structure file

This example is a geometry optimization of a capped dipeptide, where the central leucine sidechain is the QM region, and is treated at the B3LYP/6-31G* level.

```
*** Jaguar input
&gen
mmqm=1
basis=6-31G*
idft=22111
igeopt=1
$
***
*** Impact input
write file qmmm.out -
      title QMMM Energy on Leu  Dipeptide Side Chain *

create
  build primary name dipep type auto -
    read maestro file leu.mae
  build types name dipep
quit

setmodel
  setpotential
    mmechanics
  quit
  read parm file paramstd.dat noprint
  energy parm cutoff 20.0 listupdate 100 diel 1.0 nodist
  qmregion residue name dipep resn 2 molid 1 cutb 3
quit

minimize
  conjugate dx0 5.000000e-02 dxm 1.000000e+00
  input cntl mxcyc 1000 deltae 0.5
  run
  write maestro file "leu_out.mae"
quit

end
```

Input files	
`bind.inp`	Main input file
`paramstd.dat`	Energy parameter file
`prot.pdb`	Coordinate file
`lig.pdb`	Coordinate file

Output files	
`bind.out`	Main output file

This example consists of a quantum ligand in a protein with three quantum side chains.

```
***  Jaguar input
&gen
mmqm=1
basis=6-31G*
igeopt=1
$
***
***   IMPACT input
write file ligand+prot
      title QM-MM binding calc *
create
  build primary name prot type protein mole pro read file cmpx_prot_min.pdb
  build primary name prot type ligand  mole lig read file cmpx_lig_min.pdb
  read coordinates name prot mole pro brookhaven file cmpx_prot_min.pdb
  read coordinates name prot mole lig brookhaven file cmpx_lig_min.pdb
quit
setmodel
   setpotential
     mmechanics
   quit
   read parm file paramstd.dat noprint
   enrg parm cutoff 99.0 -
     listupdate 10000 diel 1.0 nodist print 10
   qmregion residue name prot  mole lig all
   qmregion residue name prot mole pro resn 23 cutb 3
   qmregion residue name prot mole pro resn 43 cutb 3
   qmregion residue name prot mole pro resn 47 cutb 3
quit
minm
  conjugate dx0 0.05 dxm 3.0
  input cntl mxcyc 10000 rmscut deltae 0.5
  run
quit
end
```

This example is a p450 heme system. Atom 44 is an oxygen atom bound to the heme, residue 417 is a camphor ligand, residue 420 is the heme group, and residue 357 with a QM/MM cut is a cysteine coordinated to the heme.

```
write file "p450.out" -
      title "p450 + camphor" *

create
  build primary name species1 type auto read maestro file "feo.mae"
  build types name species1
quit

setmodel
  setpotential
    mmechanics
  quit
  read parm file -
"paramstd.dat" -
  noprint
  energy parm dielectric 1 nodist -
   listupdate 10000000 -
   cutoff 100000
  qmregion atom name species1 atom 44
  qmregion residue name species1 resn 417 chain A  molid 1
  qmregion residue name species1 resn 420 chain A  molid 2
  qmregion residue name species1 resn 357 chain A  molid 1 cutb 3
quit

minm
  conjugate dx0 5.000000e-02 dxm 1.000000e+00
  input cntl mxcyc 1000 deltae 0.5
  run
  write maestro file -
"feo1dzp_out.mae"
quit

end
```

C.4.7 Polarizable Force Field Test

This example illustrates the usage of the polarizable force filed (PFF). It will run a minimization in fixed charge force field first (OPLS-AA), then run a minimization and a dynamics in polarizable force field.

Input files	
`pff.inp`	Main input file
`parampff.dat`	Parameter file
`1crn.pdb`	PDB coordinate file

Output files	
`pff.out`	Main output file

```
set FFIELD opls2000
```

Polarizable force field (PFF) only works with opls2000.

```
write file pff.out title pff test *
create
   build primary name pfftest type protein read file 1crn.pdb
   read coordinates name pfftest brookhaven file 1crn.pdb
   build types name pfftest
quit
! minimize in fixed charge force field first
setmodel
  setpotential
    mmechanics
  quit
  read parm file paramstd.dat noprint
  energy parm cutoff 100.0 listupdate 10 diel 1.0 nodist
quit
minm
  conjugate dx0 0.05 dxm 1.0 rest 50
  input cntl mxcyc 500 rmscut 5.0e-2 deltae 1.0e-5
  run
quit
! minimize in polarizable force field
setmodel
  setpotential
    mmechanics pff
```

Turn on PFF by simply say "mmechanics pff".

```
  quit
  read parm file parampff.dat noprint
  energy parm cutoff 100.0 listupdate 10 diel 1.0 nodist
quit
minm
  conjugate dx0 0.05 dxm 1.0 rest 50
  input cntl mxcyc 1000 rmscut 5.0e-2 deltae 1.0e-5
```

```
  run
  write pdb brookhaven name pfftest file prot_min.pdb
quit
```

Run 1000 steps of conjugate gradient minimization in PFF.

```
! dynamics in polarizable force field
dynamics
  input cntl -
       nstep 1000 delt 0.001 relax 0.1 seed 100 -
       initialize temperature at 10.0 constant temperature -
       nprnt 10 tol 1.e-7
  input target temperature 298.0
  run
  write pdb brookhaven name pfftest file prot_dyn.pdb
quit
```

Run 1000 steps of constant temperature dynamics in PFF.

```
end
```

C.4.8 Glide Example

This example runs the Glide docking module on ten conformations of the ligand from a thrombin complex, PDB code 1ETS. It uses the greedy scoring and pose refinement features of Glide, and a distance-dependent dielectric of $4r$ in energy calculations.

Caution: Glide has evolved quite significantly since this example was created. Please see the *FirstDiscovery Quick Start Guide*, *FirstDiscovery Help Guide*, and *FirstDiscovery Technical Notes* for up-to-date documentation on Glide.

The easiest way to set up Glide simulations is through the Maestro graphical interface. Using the Maestro interface has the added benefit of automatically setting up many simulation parameters to Schrödinger's recommended values.

Input files	
`1ets4r.inp`	Main input file
`1etsligref.pdb`	Initial ligand coordinate file
`1ets30a.grd`	Adaptive grid structure file
`1ets30a*.fld`	Energy grid files
`1ets30a*.save`	Rough-score grid files
`1ets30a.site`	Ligand site file
`1etslig[1-9].pdb`	conformer coordinates

Output files	
`1ets4r.out`	Main output file

```
write file 1ets4r.out title Docking inhibitor to 1ETS *
create
  build primary name drug type auto read pdb file 1etsligref.pdb
  build types name drug
quit
```

The first `dock` task sets up the calculation. We will read the Lennard-Jones energy grid from files '`1ets30a_vdw.fld`', and `rdiel` indicates reading the coulomb grid with the distance-dependent dielectric, '`1ets30a_coul2.fld`'. The `smooth anneal 1` command indicates that we read only the energy grids in these files that incorporate short-distance *smoothing*. We will read the normal rough-scoring grid from '`1ets30a.save`', the greedy grid from '`1ets30a_greedy.save`', and site information from '`1ets30a.site`'. Throughout the rough-score screening, we will keep a maximum of 200 poses, from a maximum of 10 conformations. The cutoff for the `subset score` is -60.0. We do not run screening in this task, we only set up the grids.

```
dock
  smooth anneal 1
  receptor readf 1ets30a rdiel
  ligand name drug
  screen -
   readscreen 1ets30a.save -
   readcmsite 1ets30a.site -
   greedy readgreed 1ets30a_greedy.save -
   maxkeep 200 subsc -60.0
  parameter setup save maxconf 10
  run
quit
```

Run the rough-score screening algorithm on the current ligand conformation ('`1etsligref.pdb`'), and mark it as the reference conformation. Save the grids, and results, for subsequent accumulation.

```
dock
  ligand reference name drug
  parameter   save
  screen
  run
quit
```

Loop on the index 'i', from 1 to 9.

```
put 1 into 'i'
while 'i' le 9
```

Construct the name of the ligand file for conformation 'i': 1etslig'i'.pdb.

```
    put $1etslig$ concat (char 'i') concat $.pdb$ into 'filename'
```

Read in the next conformation, but don't run atomtyping on it (`noat`), because we assume all of these files contain the same atoms in the same order.

```
create
  read coordinates noat brookhaven name drug file 'filename'
quit
```

Run screening on this conformation.

```
dock
  ligand name drug
  parameter   save
  screen
  run
quit
```

Increment the loop index.

```
  put 'i' + 1 into 'i'
endwhile
```

Run the refinement step and energy minimization, without reading in or screening a new ligand conformation. Refinement will pass at most 20 poses to energy minimization. The `smooth anneal 1` command here indicates that we run the minimization only on the *smoothed* energy surface, rather than "annealing in" the hard-core (infinite at zero distance) potentials. Energy minimization will use a dielectric coefficient of 4.0, which combined with `rdiel` above implies a distance-dependent dielectric of $4r$.

```
dock
  smooth anneal 1
  parameter   clean
  ligand keep
  screen noscore refine maxref 20
  minimize dielco 4.0
  run
quit
end
```

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